

FILE 'USPATFULL, CAPLUS, EMBASE' ENTERED AT 12:38:35 ON 28 AUG 2003

L1 1887 FILE USPATFULL  
L2 18346 FILE CAPLUS  
L3 10024 FILE EMBASE  
TOTAL FOR ALL FILES  
L4 30257 S GENISTEIN OR QUERCETIN

FILE 'USPATFULL, CAPLUS, EMBASE' ENTERED AT 12:38:41 ON 28 AUG 2003

L5 1529 FILE USPATFULL  
L6 99 FILE CAPLUS  
L7 477 FILE EMBASE  
TOTAL FOR ALL FILES  
L8 2105 S ACNE AND SCAR?  
L9 38 FILE USPATFULL  
L10 0 FILE CAPLUS  
L11 0 FILE EMBASE  
TOTAL FOR ALL FILES  
L12 38 S L4 AND L8  
L13 16319 FILE USPATFULL  
L14 6076 FILE CAPLUS  
L15 25875 FILE EMBASE  
TOTAL FOR ALL FILES  
L16 48270 S SCAR OR SCARRING OR CICATRIZATIONC  
L17 16579 FILE USPATFULL  
L18 6279 FILE CAPLUS  
L19 26162 FILE EMBASE  
TOTAL FOR ALL FILES  
L20 49020 S SCAR OR SCARRING OR CICATRIZATION  
L21 4 FILE USPATFULL  
L22 7 FILE CAPLUS  
L23 8 FILE EMBASE  
TOTAL FOR ALL FILES  
L24 19 S L20 (1S) L4  
L25 678 FILE USPATFULL  
L26 51 FILE CAPLUS  
L27 351 FILE EMBASE  
TOTAL FOR ALL FILES  
L28 1080 S L16 (1S) ACNE?  
L29 15 FILE USPATFULL  
L30 0 FILE CAPLUS  
L31 0 FILE EMBASE  
TOTAL FOR ALL FILES  
L32 15 S L28 AND L4  
SAVE ALL LSCARMMP/L

L12 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN  
AN 1985:481706 CAPLUS  
DN 103:81706  
TI Prevention and treatment of **scars** with enzymes  
IN Pinnell, Sheldon R.  
PA Bio-Specifics N. V., Neth.  
SO U.S., 4 pp.

CODEN: USXXAM

DT Patent  
LA English  
IC ICM A61K037-48  
NCL 424094000

CC 1-12 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4524065	A	19850618	US 1983-520203	19830804
	US 4645668	A	19870224	US 1985-716742	19850327
PRAI	US 1983-520203		19830804		

AB The enzyme **collagenase** [9001-12-1] and the **collagenase** -hyaluronidase mixt. [97726-75-5] were used for the prevention of an for the dissoln. of mammalian cicatrices such as **acne scars**, keloids, and other hypertrophic **scars** in human subjects after intralesional administration.

ST **scar** treatment prevention **collagenase** hyaluronidase

IT Skin, disease or disorder

(**scar**, prevention and treatment of, with **collagenase** and hyaluronidase, in humans)

IT 9001-12-1 97726-75-5

RL: BIOL (Biological study)

(**scars** prevention and treatment with, in humans)

=>

L3 ANSWER 8 OF 10 USPATFULL on STN

SUMM The present invention relates to an anhydrous, stable retinol-  
or vitamin A-based cosmetic or pharmaceutical composition for the skin  
and to the use thereof for the treatment of skin disorders, in  
particular for the treatment of acne, keratinization or  
scarring problems, light-related aging, and the prevention and  
softening of wrinkles.

ACCESSION NUMBER: 2000:7069 USPATFULL  
TITLE: Anhydrous stable retinol based cosmetic or  
pharmaceutical composition  
INVENTOR(S): Segot, Evelyne, Nogent sur Morne, France  
Laugier, Jean-Pierre, Antony, France  
PATENT ASSIGNEE(S): L'Oreal, Paris, France (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6015568		20000118
APPLICATION INFO.:	US 1996-627480		19960404 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1994-317879, filed on 4 Oct 1994, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1993-11850	19931005
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Page, Thurman K.	
ASSISTANT EXAMINER:	Berman, Alysia	
LEGAL REPRESENTATIVE:	Nixon & Vanderhye P.C.	
NUMBER OF CLAIMS:	7	

preparation. U.S. Pat. No. 4,847,084 discloses two ointments for treatment of decubitus ulcers, Decubitane #1 and #2, which are based upon a debriding enzyme, fibrinolysin, with additives including chlorophyll and povidoneiodine. U.S. Pat. No. 3,622,668 discloses a scar-inhibiting lotion for treatment of livestock injuries which contains phenol, retinol, ergosterol and olive oil, or fish oil. None of the disclosed or claimed "comfrey" treatment formulations for humans or other mammals are foams, controlled-release particles, controlled-release implants, emulsions, vesicles, liposomes, aerosols or micelles.

ACCESSION NUMBER: 94:62220 USPATFULL  
 TITLE: Polyphase fluid extraction process, resulting products and methods of use  
 INVENTOR(S): Steuart, Gary M., 98 Viking Terr., Northfield, MN, United States 55057  
 Huffstutler, Jr., M. Conrad, 6200 Lynn La., Lago Vista, TX, United States 78645

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5330756		19940719
APPLICATION INFO.:	US 1992-980839		19921124 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1990-599616, filed on 18 Oct 1990, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Azpuru, Carlos		
LEGAL REPRESENTATIVE:	Huffstutler, Jr., M. Conrad		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	847		

L7 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN

IT 117-39-5, **Quercetin** 153-18-4, Rutin 520-26-3, Hesperidin  
 1340-08-5, Citrin 9004-61-9, Hyaluronic acid 10236-47-2, Naringin  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES  
 (Uses)  
 (bioflavonoids for retardation of skin aging)

IT 9001-12-1, **Collagenase** 37326-33-3, Hyaluronoglucosaminidase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (inhibitors; bioflavonoids for retardation of skin aging)

ACCESSION NUMBER: 1995:618220 CAPLUS  
 DOCUMENT NUMBER: 123:17505  
 TITLE: Bioflavonoids for retardation of skin aging  
 INVENTOR(S): Backhaus, Erwin  
 PATENT ASSIGNEE(S): Germany  
 SOURCE: Ger. Offen., 2 pp.  
 CODEN: GWXXBX

DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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DE 4339486	A1	19950524	DE 1993-4339486	19931119
PRIORITY APPLN. INFO.:			DE 1993-4339486	19931119

L7 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN

AB Flavones or anthocyanins as matrix metalloprotease inhibitors and their extn. from medicinal plants (e.g. Scutellaria baicalensis roots) for therapeutic use are claimed. Baicalein inhibited the activity of matrix metalloprotease (e.g collagenase) with IC50 = 25 .mu.g/mL. The flavones or anthocyanins may be used for treating deformative arthropathy, gingivitis, cancer metastasis, and chronic rheumatism.

IT 90-18-6P, Quercetagenin 117-39-5P, Quercetin 134-04-3P, Pelargonidin 480-40-0P, Chrysin 491-67-8P, Baicalein 491-70-3P, Luteolin 520-18-3P, Kaempferol 520-36-5P, Apigenin 528-53-0P, Delphinidin 528-58-5P, Cyanidin 529-44-2P, Myricetin 529-53-3P, Scutellarein 18003-33-3P, 6-Hydroxyluteolin

RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(flavones or anthocyanins as matrix metalloprotease inhibitors and their extn. from plants for therapeutic use)

IT 9001-12-1P, Collagenase 37259-58-8P, Serine proteinase 81669-70-7P, Metalloprotease 146480-36-6P, Gelatinase B

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(inhibitors; flavones or anthocyanins as matrix metalloprotease inhibitors and their extn. from plants for therapeutic use)

ACCESSION NUMBER: 1996:417847 CAPLUS

DOCUMENT NUMBER: 125:67741

TITLE: Flavones or anthocyanins as matrix metalloprotease inhibitors and their extraction from medicinal plants for therapeutic use

INVENTOR(S): Kumagai, Kazuo; Fujiwara, Fumi; Negoro, Takaatsu; Kaneoka, Shoji; Saji, Kitao

PATENT ASSIGNEE(S): Sumitomo Pharma, Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.  
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08104628	A2	19960423	JP 1994-266264	19941004
PRIORITY APPLN. INFO.:			JP 1994-266264	19941004
OTHER SOURCE(S):		MARPAT 125:67741		

side showed a greatly thickened epidermis and an increased number of new blood vessels using the conventional haemotoxylin and eosin technique. A special stain (Hale) showed increased glycosaminoglycans. Van Gieson's stain showed deeper staining of the collagen bundles, reflecting increased synthesis of collagen. Moreover, a moderate inflammatory reaction in the fibrous septa dividing the fat compartments of the subcutaneous tissue was eliminated on the retinoic acid side. Fibrosis (scarring) was also reduced.

CLM

What is claimed is:

1. A method for retarding and reversing cellulite, comprising topically applying to human **skin** a **retinoid** in an amount and for a period of time effective to retard and reverse cellulite, said amount being insufficient to be excessively irritating.

2. The method according to claim 1, wherein the **retinoid** is present in an emollient vehicle.

3. The method according to claim 1, wherein the amount of **retinoid** is an amount equivalent to about 0.01% to about 0.25% **retinoic acid** by weight concentration.

4. The method according to claim 2, wherein the amount of **retinoid** in the emollient vehicle is an amount equivalent to about 0.05% to about 0.1% **retinoic acid** by weight concentration.

5. The method according to claim 1, wherein the **retinoid** is applied in a once daily dosage.

6. The method according to claim 1, wherein the **retinoid** is applied in a twice daily dosage.

7. A method according to claim 1, wherein said **retinoid** is selected from the group consisting of **retinoic acid**, **retinoic acid** derivatives and stereoisomers thereof.

8. A method according to claim 7, wherein said **retinoid** comprises **retinoic acid**.

9. A method of preventing recurrence of cellulite in patients in which the effects of cellulite has been retarded and reversed, comprising topically applying to human **skin** of said patients a **retinoid** in an amount and for an indefinite maintenance period of time effective to prevent cellulite, said amount being insufficient to be excessively irritating.

10. The method according to claim 9, wherein the **retinoid** is present in an emollient vehicle.

11. The method according to claim 9, wherein the amount of **retinoid** is an amount equivalent to about 0.01% to about 0.25% **retinoic acid** by weight concentration.

12. The method according to claim 10, wherein the amount of **retinoid** in the emollient vehicle is an amount equivalent to about 0.05% to about 0.1% **retinoic acid** by weight concentration.

13. A method according to claim 9, wherein said **retinoid** is selected from the group consisting of **retinoic acid**, **retinoic acid** derivatives and stereoisomers thereof.

14. A method according to claim 13, wherein said **retinoid** comprises **retinoic acid**.

L15 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:796565 CAPLUS

DN 128:7221

TI Ointment for prevention of facial **scarring** and blemishes of the face and body

PA Puyravaud, Michelle, Fr.

SO Fr. Demande, 6 pp.

CODEN: FRXXBL

DT Patent

LA French

IC ICM A61K007-48

CC 62-4 (Essential Oils and Cosmetics)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2743720	A1	19970725	FR 1996-754	19960123
	FR 2743720	B1	19980410		
PRAI	FR 1996-754		19960123		

AB An ointment is disclosed for use in prevention of sequelae of **scarring** of the face and for treatment of blemishes of the face and body such as **acne** and mini-cysts. Thus, an ointment is formulated which is comprised (in grams) of washed sulfur 2.5-5.0, salicylic acid 2.0-5.0, and essential oils, including borneol 1.0-3.0, cypress oil 0.100-0.150, geranium essential oil 0.100-0.150, lavender oil 0.100-0.150, grapefruit oil 0.100-0.150, patchouli oil 0.100-0.150, rose oil 0.100-0.150, sassafras oil 0.100-0.150, and ylang-ylang 0.100-0.150.

ST skin ointment **acne scarring** facial blemish

IT Essential oils

RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses) (cypress; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Head

(face; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils

RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses) (geranium; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils

RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses) (grapefruit; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT **Acne**

(inhibitors; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils

RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses) (lavender; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Cosmetics

**Keloid**

Ylang-ylang (Cananga odorata)

(ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils

RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses) (ointment for prevention of facial **scarring** and blemishes of the face and body)



IT Essential oils  
RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)  
(patchouli; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils  
RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)  
(rose; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT Essential oils  
RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)  
(sassafras; ointment for prevention of facial **scarring** and blemishes of the face and body)

IT 507-70-0, Borneol  
RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)  
(ointment for prevention of facial **scarring** and blemishes of the face and body)

IT 7704-34-9, Sulfur, biological studies  
RL: BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)  
(washed; ointment for prevention of facial **scarring** and blemishes of the face and body)

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## keloid

<dermatology> A sharply elevated, irregularly shaped, progressively enlarging scar due to the formation of excessive amounts of collagen in the corium during connective tissue repair.

Origin: Gr. Kel = tumour, eidos = form

(18 Nov 1997)

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**Previous:** [Kelly clamp](#), [Kelly, Howard](#), [Kelly's operation](#), [Kelly's rectal speculum](#)

**Next:** [keloidosis](#), [keloplasty](#), [kelosomia](#), [kelotomy](#), [kelp](#), [kelpfish](#), [kelpy](#)

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## hypertrophic scar

An elevated scar resembling a keloid but which does not spread into surrounding tissues, is rarely painful, and regresses spontaneously; collagen bundles run parallel to the skin surface.

(05 Mar 2000)

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**Previous:** [hypertrophic pyloric stenosis](#), [hypertrophic rhinitis](#), [hypertrophic rosacea](#)

**Next:** [hypertrophied](#), [hypertrophied lenticels](#), [hypertrophy](#)

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## cicatrix

The formation of new tissue in the process of wound healing.

(12 Dec 1998)

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**Previous:** [cicatricial horn](#), [cicatricial pemphigoid](#), [cicatricotomy](#), [cicatriscation](#)

**Next:** [cicatrix](#), [hypertrophic](#), [cicatrizant](#), [cicatrizacion](#)

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## cicatrizzation

1. The process of scar formation.
2. The healing of a wound otherwise than by first intention.

(05 Mar 2000)

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**Previous:** [cicatricotomy](#), [cicatrissation](#), [cicatritz](#), [cicatritz](#), [hypertrophic](#), [cicatrizant](#)

**Next:** [cicatrizatiz atelectasis](#), [ciclopirox olamine](#), [cicutoxin](#), [cidofovir](#)

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SUMM There is increasing interest in introducing vitamins such as vitamins A, B, C, D, E and F (essential fatty acids), as well as other active agents, into cosmetic and/or dermatological compositions with a view to providing specific treatments against, for example, excessive weight, skin aging, dry skin, skin pigmentation, acne and certain skin diseases (psoriasis) or, alternatively, in order to promote the cicatrizization (scar formation) and/or restructuring of the skin.

DETD As a further example, it is possible to use the glucosyl derivative of quercetin as a first precursor and a quercetin ester such as quercetin ferulate as a second precursor, in order to liberate quercetin synergistically on application to the skin of a composition containing this pair of precursors.

CLM What is claimed is:

9. The composition of claim 8, wherein said first precursor is a C.sub.3 to C.sub.6 vitamin or quercetin monosaccharide, and said second precursor is selected from the group consisting of ascorbic acid phosphates, retinol phosphates, tocopherol nicotinate, retinol palmitates, ascorbic acid palmitates, tocopherol acetates, retinol acetates, ascorbic acid acetates, retinol propionates, ascorbic acid propionates, quercetin palmitates, quercetin acetates, quercetin propionates, quercetin ferulates, and mixtures thereof.

23. The composition of claim 22, wherein said skin active agent is selected from the group consisting of vitamin A, vitamin C, vitamin E, lactic acid, quercetin and retinol.

PI

US 5607921

19970304

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L29 ANSWER 2 OF 5 USPATFULL on STN

DETD [0070] Agents may include, without limitation, the following compositions and derivatives and analogs thereof: hair dyes, vegetable dyes, food coloring, fabric dyes, tissue stains, shoe or leather dyes, other plant products (such as flavonols, chlorophyll, copper chlorophyllin, bacteria chlorophylls, carotenoids, lycopene, enzymes, monoclonal antibodies, any immunological agent, genetically engineered agent, benign infectious agents, whether naturally occurring or genetically engineered (e.g. the bacteria that normally reside on the skin such as acne bacteria, etc.), antibiotics, agents which attach to sebocytes in the sebaceous gland or duct cells directly, whether by topical or systemic agents that localize in these target tissues, including antibodies or antibody-chromophore compounds of these structures. In general, the topical agent chosen will have certain absorption characteristics that augment the penetration of the radiation to the tissue targeted for treatment, i.e., sebaceous oil gland, acne-scarred tissue, etc.

DETD [0084] ~~Scarring is commonly seen as a consequence of disorders, diseases, or dysfunctions of the sebaceous apparatus.~~ Scarring may consist of one or more of the following: raised hypertrophic scars or fibrosis, depressed atrophic scars, hyperpigmentation, hyperpigmentary redness or telangectasia. Raised or thick or hard hypertrophic scars (which are composed of an excess of collagen) can be improved by photomodulation wherein the stimulation of production of collagen dissolving enzymes (called Matrix metalloproteinases) such as MMP-1 (collagenase) causes the scar tissue to be diminished. Such photomodulation can be accomplished alone or in combination with photothermal methods (see FIGS. 14-38) wherein MMP-1 can be seen to be increased by the traditional photothermal methods--at around 7.0J/cm<sup>2</sup> energy levels, although MMP-1 also can be stimulated in the non thermal photomodulation light energies) FIG. 13 shows enlarged tissue photographs of new collagen growth produced by the present invention.

ACCESSION NUMBER: 2003-4510 USPATFULL

TITLE: Low intensity light therapy for the manipulation of fibroblast, and fibroblast-derived mammalian cells and collagen

INVENTOR(S): McDaniel, David H., Virginia Beach, VA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003004556	A1	20030102
APPLICATION INFO.:	US 2002-119772	A1	20020411 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-819081, filed on 15 Feb 2001, PENDING Division of Ser. No. US 1998-203178, filed on <u>30 Nov 1998</u> , <u>GRANTED, Pat. No. US 6283956</u>		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Wayne C. Jaeschke, Jr., Morrison & Foerster LLP, Suite 5500, 2000 Pennsylvania Avenue, N.W., Washington, DC, 20006-1888		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	38 Drawing Page(s)		
LINE COUNT:	2030		

=>

L35 ANSWER 2 OF 192 CAPLUS COPYRIGHT 2003 ACS on STN  
 AN 2002:251940 CAPLUS  
 DN 136:241710  
 TI Treatment of **acne** using lipoic acid  
 IN Perricone, Nicholas V.  
 PA USA  
 SO U.S., 7 pp., Cont.-in-part of U.S. Ser. No. 415,792.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 IC ICM A61K031-38  
 ICS A61K031-355; A61K031-045; A61K031-07  
 NCL 514448000  
 CC 1-12 (Pharmacology)  
 Section cross-reference(s): 62  
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6365623	B1	20020402	US 1999-475514	19991230
	US 5965618	A	19991012	US 1997-971820	19971117
	US 6472432	B1	20021029	US 1999-415792	19991008
	WO 2001049250	A2	20010712	WO 2001-US63	20010102
	WO 2001049250	A3	20020110		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	BR 2001004872	A	20020213	BR 2001-4872	20010102
	EP 1185257	A2	20020313	EP 2001-901666	20010102
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
	JP 2003519165	T2	20030617	JP 2001-549619	20010102
PRAI	US 1997-971820	A2	19971117		
	US 1999-415792	A2	19991008		
	US 1999-475514	A	19991230		
	WO 2001-US63	W	20010102		
AB	Active <b>acne</b> and <b>acneiform</b> scars are treated by topical application of a compn. contg. lipoic acid and/or a lipoic acid deriv. such as dihydrolipoic acid, a lipoic or dihydrolipoic acid ester, a lipoic or dihydrolipoic acid amide, a lipoic or dihydrolipoic acid salt, and mixts. of any of these to <b>reduce</b> erythema, pore size, and <b>scarring</b> . Topical application of lipoic acid and/or a lipoic acid derivs. are advantageously used with at least one adjunct ingredient such as a <b>retinoid</b> , an antibiotic, or benzoyl peroxide conventionally used for <b>acne</b> , alone or in combination with dimethylamino alc., an .alpha.-hydroxy acid such as glycolic acid, a tyrosine, tocotrienol, and/or a fatty acid ester of ascorbic acid. One preferred embodiment contains a combination of lipoic acid, an .alpha.-hydroxy acid, and dimethylamino alc. In an example given use of a lipoic acid or lipoic + glycolic acid preps. by patients with <b>acne vulgaris</b> and/or <b>acneiform scars</b> markedly <b>reduced</b> erythema, pustules, papules and comedones.				
ST	<b>acne</b> treatment lipoate glycolate dimethylaminoethanol				
IT	Alcohols, biological studies				
	RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (amino; treatment of <b>acne</b> using lipoic acid in combination with an .alpha.-hydroxy acid and dimethylamino alc.)				



L27 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN

IT **Flavonoids**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(bio-, Ginkgo; topical medicament contg. compds. with vasokinetic  
activity for ~~treatment of wounds and scars~~)

IT **Flavonoids**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(oxo, Ginkgo biloba; topical medicament contg. compds. with vasokinetic  
activity for **treatment** of wounds and scars)

AN 1995:997258 CAPLUS

DN 124:66591

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 680761	A1	19951108	EP 1995-105944	19950420
	EP 680761	B1	20011219		
	R: DE, ES, FR, GB, IT, SE				
	ES 2080037	T3	20020701	ES 1995-105944	19950420
	JP 08040876	A2	19960213	JP 1995-108720	19950502
	CA 2148632	AA	19951107	CA 1995-2148632	19950504
	AU 9517886	A1	19951116	AU 1995-17886	19950504
	AU 710197	B2	19990916		
	<b>US 5795575</b>	A	19980818	US 1996-763925	19961212
	HK 1012568	A1	20020726	HK 1998-113939	19981217

L27 ANSWER 4 OF 9 USPATFULL on STN

DETD [0023] Our invention teaches that cellulites may be treated effectively by using biochemical agents that are derived from plants which are capable of selectively blocking the action of endogenous estrogen and stimulating lipolysis. Specifically, the use of **genistein** blocks the action of estradiol on the estrogen receptor in the fibroblast of the connective tissue. More specifically, this receptor appears to be the estrogen receptor .beta.. By blocking this receptor, the fibroblasts in the area of the cellulite will not be stimulated to produce more **collagenase** and elastase. This action allows the body to affect a repair of the damaged connective tissue. At the same time, **genistein** is capable of stimulating lipolysis in the area of cellulite..sup.6 **Genistein** is known to inhibit tyrosine kinase which promotes the formation of the matrix metalloprotein **collagenase** from fibroblasts..sup.7 .sup.6Kuppusamy, U R, and Das, N P. Effects of flavanoids on cyclic AMP phosphodiesterase and lipid mobilizations in rat adipocytes. Biochem Pharmacol 44:1307-1315, 1992. .sup.7Akiyama, T et al **Genistein** a specific inhibitor of tyrosine kinase. J. biol Chem 262:5592-5, 1987.

DETD [0026] 1. An isoflavone, such as **genistein**, diadzein, or other isoflavones, that have an affinity for estrogen receptors on fibroblasts. The competitive action blocks the stimulation of estrogen to produce **collagenase**.

ACCESSION NUMBER: 2002:198294 USPATFULL  
 TITLE: Formulation of flavones and isoflavones for treatment of cellulite  
 INVENTOR(S): Pugliese, Peter T., Berneville, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106388	A1	20020808
APPLICATION INFO.:	US 2001-989019	A1	20011121 (9)

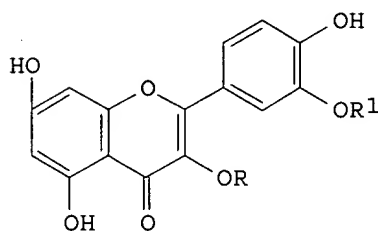
	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-250397P	20001124 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ARTHUR R. EGLINGTON, 113 Cross Creek Dr. R.D. # 5., Pottsville, PA, 17901	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	444	

L6 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2002 ACS  
AN 1984:451606 CAPLUS  
DN 101:51606  
TI Interaction in the antibacterial activity of flavonoids from *Sophora japonica* L. to *Propionibacterium*  
AU Kimura, Masayuki; Yamada, Hiromi  
CS Yakult Inst. Microbiol. Res., Kunitachi, 186, Japan  
SO Yakugaku Zasshi (1984), 104(4), 340-6  
CODEN: YKKZAJ; ISSN: 0031-6903  
DT Journal  
LA Japanese  
CC 10-5 (Microbial Biochemistry)  
Section cross-reference(s): 63  
AB The antibacterial activities of several crude drugs to bacteria were examd. by the agar diffusion method using paper disks, and it was found that the EtOH ext. of flower buds of *S. japonica* showed antibacterial activity against *P. acnes*, *P. avidum*, and *Staphylococcus aureus* under weak acidic conditions. After purifn. of the ext., the activity was attributed to the interaction caused by 3 components: **quercetin** (I), rutin (II), and isorhamnetin-3-rutinoside (III). When I, II, and III were applied singly, only I showed very weak activity, and the others not at all. By mixing I and II, or I and III, 50% and 70% activity of the EtOH ext. appeared, resp. Moreover, after mixing the 3 flavonoids, the full activity of the ext. was recovered. A small amt. of kaempferol-3-rutinoside was also obtained from the EtOH ext. This compd. had a similar effect to III but was weaker. Examn. of the drug interaction in a liq. culture system showed that the antibacterial activity of the system increased with an increase in the soly. of I caused by II. Thus, the active principle is I, and by the addn. of II, the soly. of I increases to increase the apparent activity. A similar increase in the activity of I by the addn. of III is thought to be based on the same mechanism as that of II.  
ST *Sophora* flavonoid bactericide *Propionibacterium*  
IT *Sophora japonica*  
(flavonoids from flower bud ext. of, antibacterial activity of)  
IT *Propionibacterium acnes*  
*Propionibacterium avidum*  
*Staphylococcus aureus*  
(flavonoids of *Sophora japonica* flower buds sensitivity to)  
IT Microbicidal and microbiostatic action  
(bactericidal, of flavonoids, soly. in relation to)  
IT Glycosides  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(flavonoid, antibacterial activity of, to *Propionibacterium*)  
IT 153-18-4 604-80-8 17650-84-9  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(antibacterial activity of quercetin and, soly. in relation to)  
IT 117-39-5  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(antibacterial activity of, soly. in relation to)

ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

AN 1984:460134 CAPLUS  
 DN 101:60134  
 TI Skin lotions for treatment of Propionibacterium acnes  
 PA Yakult Honsha Co., Ltd., Japan  
 SO Jpn. Kokai Tokkyo Koho, 5 pp.  
 CODEN: JKXXAF  
 DT Patent  
 LA Japanese  
 IC A61K031-35; A61K007-00; A61K031-70  
 ICA C07D311-30; C07H017-06  
 CC 63-6 (Pharmaceuticals)  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 59044313	A2	19840312	JP 1982-154598	19820907
GI	JP 02001806	B4	19900112		



I, R=R<sup>1</sup>=H

II, R=?-rhamnosyl-?-glucosyl, R<sup>1</sup>=H

III, R=?-rhamnosyl-?-glucosyl, R<sup>1</sup>=Me

AB Microbicidal formulations, esp. effective against P. **acnes** on the skin, contain **quercetin** (I) [117-39-5] in combination with rutin (II) [153-18-4] and/or isorhamnetin 3-O-rutinoside (III) [604-80-8]. Thus, I 0.6, II 2.0, and III 0.4 g were dissolved in a mixt. of 70 mL EtOH and 30 mL 0.05M .alpha.-hydroxybutyrate buffer (pH 5.0) to obtain a skin lotion.

ST quercetin isorhamnetin rutin microbicide; Propionibacterium quercetin isorhamnetin rutin; acne flavonoid

IT Propionibacterium acnes  
 (control of, quercetin and isorhamnetin rutinoside and rutin for)

IT Acne  
 (treatment of, with skin lotion contg. isorhamnetin rutinoside and quercetin and rutin)

IT 153-18-4  
 RL: BIOL (Biological study)  
 (skin lotion contg. isorhamnetin rutinoside and quercetin and, for acne treatment)

IT 117-39-5  
 RL: BIOL (Biological study)  
 (skin lotion contg. isorhamnetin rutinoside and rutin and, for acne treatment)

IT 604-80-8  
 RL: BIOL (Biological study)  
 (skin lotion contg. quercetin and rutin and, for acne treatment)

L13 ANSWER 14 OF 71 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 1991:17588 CAPLUS  
 DOCUMENT NUMBER: 114:17588  
 TITLE: Sebaceous gland-inhibiting isoflavones  
 INVENTOR(S): Jokura, Yoji; Ishikawa, Shinji; Nishizawa, Yoshinori;  
 Yoshimura, Koichi; Kitahara, Takashi; Hattori,  
 Michihiro  
 PATENT ASSIGNEE(S): Kao Corp., Japan  
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.  
 CODEN: JKXXAF  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Japanese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 02193919	A2	19900731	JP 1989-13481	19890123

OTHER SOURCE(S): MARPAT 114:17588

AB Sebaceous gland-inhibiting agents contain isoflavones I (R1, R2, R3 = H, aliph. or cyclic hydrocarbyl, C1-6 alkoxy; A, B, C, D = H, OH, MeO; R2 = C .noteq. H) as active ingredients. I control excess sebum secretion, thus preventing **acne**, and have minimal side effects even after prolonged use. Aq. acetone soln. contg. 10.0 mg luteone/mL applied topically to hamsters at 50 .mu.L 2 times/day for 4 days resulted in remarkable inhibition of testosterone propionate-induced sebum secretion. A cosmetic prepn. was formulated contg. glycerin ether 1.50, polyoxyethylene hydrogenated castor oil 1.50, sorbitan monostearate 1.00, squalane 10.00, dipropylene glycol 5.00, **genistein** 0.10, and H2O to 100% by wt.

ST sebaceous gland inhibitor isoflavone; **acne** treatment isoflavone; **genistein acne** treatment

IT **Acne**  
 (treatment of, isoflavones for)

IT **446-72-0, Genistein** 548-77-6, Tectorigenin  
 1156-78-1, 2'-Hydroxygenistein 41743-56-0, Luteone  
 RL: BIOL (Biological study)  
 (sebaceous gland-controlling agents contg.)

=>

L13 ANSWER 13 OF 71 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:209989 CAPLUS

DOCUMENT NUMBER: 124:241803

TITLE: Skin-conditioning compositions containing isoflavone

INVENTOR(S): Brunke, Reinhold A.

PATENT ASSIGNEE(S): New Standard GmbH, Germany

SOURCE: Ger. Offen., 4 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	DE 4432947	A1	19960321	DE 1994-4432947	19940916
	DE 4432947	C2	19980409		
AB	Skin care compns. contg. isoflavone and its derivs. act as radical scavengers which prevent aging of the skin, as dermal angiogenesis inhibitors, and as antiproliferative agents against melanomas, and are useful for treatment of varicose veins, <b>acne</b> , fatty skin, graying of the hair, pigment spots, and alopecia. Thus, a gel for treatment of <b>acne</b> was prepd. by combining a mixt. of Eumulgin B1 3, Cetiol 868 10, methylparaben 0.15, propylparaben 0.10, and soybean ext. (source of isoflavones) 10.0 wt.% with H2O 73, Sepigel 305 3.5, and Kathon CG 0.05 wt.%.				
ST	skin conditioner isoflavone; <b>acne</b> treatment isoflavone; angiogenesis skin isoflavone; baldness treatment isoflavone				
IT	<b>Acne</b> Alopecia (treatment of; skin-conditioning compns. contg. isoflavones)				
IT	<b>446-72-0</b> , 5,7,4'- <b>Trihydroxyisoflavone</b> 480-23-9, 3',4',5,7-Tetrahydroxyisoflavone 486-66-8, 7,4'-Dihydroxyisoflavone 491-80-5, 5,7-Dihydroxy-4'-methoxyisoflavone 529-59-9, Genistin 529-60-2 548-76-5 552-66-9, Daidzin 574-12-9, Isoflavone 574-12-9D, Isoflavone, derivs. 2284-31-3 34086-51-6 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses) (skin-conditioning compns. contg. isoflavones)				

DETD The compounds in this invention can also be given orally in combination with compounds that bind or modify the activity of the vitamin D receptor or in combination with compounds that bind or modify the activity of the **retinoid** X receptors or **retinoic** acid receptors to provide for a synergistic effect in the treatment or prevention of the disorders listed in Tables II, III, IV, V, VI & VII. Examples of such compounds that provide for synergistic effect when given in combination with the drugs encompassed by the current invention include vitamin D analogs, various **retinoic** acid derivatives, and other ligands for **retinoid** X receptors or **retinoic** acid receptors including but not limited to compounds such as LG100268, tazarotene, TTNPB, or LGD1069 (Targretin), and RXR/PPAR heterodimeric ligands, e.g. LG101754 (Ligand Pharmaceuticals) (see, U.S. Pat. No. 6,004,987 Demarchez, et. al., Dec. 21, 1999, Use of ligands which are specific for RXR receptors.).

DETD In certain aspects, the compounds in the invention can also be given systemically (oral administration preferred) or topically in combination with natural or synthetic ligands (agonist or antagonist ligands) that bind and modify the activity of the estrogen (nuclear) receptor (ER), which include the alpha and/or the beta isoforms, i.e. ER-alpha or ER-beta or both ER-alpha and ER-beta. Examples of ER-alpha and/or ER-beta ligands are: estradiol, selective (synthetic) estrogen receptor modulators such as raloxifene, anti-estrogens such as tamoxifen and hydroxytamoxifen, and the naturally occurring phytoestrogens such as the isoflavones **genistein**, diadzein and glycitein.

DETD Synergistic therapeutic effects can be achieved by oral administration of the drugs encompassed in the current invention together with orally or intravenously administered drugs that bind to and or modify the activity of either the vitamin D receptor or **retinoid** X receptors or **retinoic** acid receptors. As such, in another embodiment, the present invention relates to a method of treating a PPAR.gamma. mediated disease, comprising administering a combination therapy of a compound of Formulae I, II or III and a member selected from the group consisting of a drug that bind to or modifies the activity of a vitamin D receptor, a **retinoid** X receptor, or a **retinoic** acid receptor.

DETD A preferred dosage range for administration of a **retinoic** acid derivative or **retinoid** would typically be from 0.1 to 100 mg per square-meter of body surface area, depending on the drug's ability to bind to or modify the activity of its cognate nuclear receptor, given in single or divided doses, orally or by continuous infusion, two or three times per day. For synergistic therapy, the preferred dosages and routes and frequency of administration of the vitamin D analogs or **retinoid** compounds can be similar to the dosages and routes and frequency of administration ordinarily recommended for these agents when given without compounds of Formulae I, II or III. Examples of effective **retinoids** are 9-cis-**retinoic** acid, 13-cis-**retinoic** acid, all-trans-**retinoic** acid (at-RA).

Preferred **retinoids** for this purpose would include 13-cis-**retinoic** acid, tazarotene, or Targretin. A preferred dosage range for systemic administration of a vitamin D analog would typically be from 0.1 to 100 mg per square-meter of body surface area, depending on the drug's ability to bind to and or activate its cognate vitamin D receptor, given in single or divided doses, orally or by continuous infusion, two or three times per day. Examples of effective vitamin D analogs are 1,25-dihydroxy-vitamin D (1,25-(OH)<sub>2</sub>-vit D) and calcipotriene. The dosage range and routes and frequency of administration of compounds of Formulae I, II or III required to achieve synergistic effects when given with vitamin D or **retinoid** derivatives are the same as those described elsewhere in this disclosure. The preferred mode of administration of these drugs for synergistic therapeutic purposes would be orally although alternatively

one can use topical or parenteral routes of administration. Synergistic therapeutic effects can also be achieved for conditions that are treated by topical administration of vitamin D derivatives or **retinoid** related compounds such as psoriasis, **acne**, or other disorders not involving the skin described in Tables II, III, V, VI & VII. The dosages and the modes and frequency of administration of the vitamin D or **retinoid** related compounds for synergistic topical therapy would be similar to those ordinarily recommended for these agents when given without compounds of Formulae I, II or III. The dosage range and the modes and frequency required for topical administration of the compounds of Formulae I, II or III given in combination with vitamin D or **retinoid** related compounds are the same as those described elsewhere in this disclosure.

DETD A patient having dermal manifestations of either psoriasis vulgaris, or **acne** vulgaris, or human papilloma virus (HPV) infection (e.g., anogenital warts) is selected for therapy using the invention. A compound of Formulae I, II or III that modifies the activity of PPAR. $\gamma$  is prepared in a cream vehicle at a concentration of 1 to 5% (weight/volume), typically 2.5% and is applied to the affected skin three times a day. After the skin lesions have subsided, therapy is discontinued.

DETD A patient having type 2 diabetes mellitus, or chronic generalized **acne**, or chronic generalized psoriasis, with or without psoriatic arthritis, or rheumatoid arthritis, or inflammatory bowel disease (e.g., ulcerative colitis) is selected for therapy. The patient weighs 80 kilograms. For infants or children the doses suggested are lowered in a linear fashion based on body weight or surface area. The female patient of child-bearing potential is given a pregnancy test to confirm that the patient is not pregnant. Provided that the patient is not pregnant and does not plan to become pregnant during treatment, a compound of Formulae I, II or III that modifies the activity of PPAR. $\gamma$  is orally administered in a dosage of 20 to 1,000 milligrams twice daily, more typically 100 mg twice daily. The patient is monitored for improvement in the manifestations of the index disease. Additionally, a complete blood count, including white cell count and differential, a platelet count, and liver function tests (such as levels of alkaline phosphatase, lactose dehydrogenase, and transaminases) are checked prior to treatment and periodically thereafter. The dosage is tapered when the manifestations of the disease subside, or discontinued if indicated.

DETD

#### TABLE II

Examples of non-malignant proliferative, inflammatory disorders treatable with compounds described in this invention  
Organ System Disease/Pathology

Dermatological Psoriasis (all forms), **acne** vulgaris, **acne** rosacea,

common warts, anogenital (venereal) warts, eczema; lupus associated skin lesions; acute and chronic dermatitides (inflammation of the skin) such as acute and chronic eczema such as atopic dermatitis, allergic dermatitis, contact dermatitis, cosmetic dermatitis, chemical dermatitis, diaper rash, sunburn, seborrheic dermatitis and solar dermatitis; keratoses such as seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging and wrinkle formation including photo-induced skin aging, keratosis follicularis; keloids and prophylaxis against keloid formation; leukoplakia, lichen planus, keratitis, urticaria, pruritus, hidradenitis, **acne** inversa.

Cardiovascular Congestive heart failure, endarteritis, endocarditis, atherogenesis, hypertension, vasculo-occlusive



diseases including atherosclerosis, thrombosis and restenosis after angioplasty; acute coronary syndromes such as unstable angina, myocardial infarction, ischemic and non-ischemic cardiomyopathies, post-MI cardiomyopathy and myocardial fibrosis, substance-induced cardiomyopathy.

Endocrine Insulin resistant states including obesity, diabetes mellitus (types 1 & 2), diabetic retinopathy, macular degeneration associated with diabetes, gestational diabetes, impaired glucose tolerance, polycystic ovarian syndrome; osteoporosis, osteopenia, accelerated aging of tissues and organs including Werner's syndrome and Wasting syndrome (all etiologies).

Urogenital Endometriosis, benign prostatic hypertrophy, leiomyoma, polycystic kidney disease, diabetic nephropathy.

Pulmonary Asthma, chronic obstructive pulmonary disease (COPD), reactive airway disease, pulmonary fibrosis, pulmonary hypertension.

Immunological/ Rheumatoid arthritis, Raynaud's phenomenon/disease, Connective tissue/ Sjogren's syndrome systemic sclerosis, systemic lupus Joints erythematous, vasculitides, ankylosing spondylitis, osteoarthritis, reactive arthritis, psoriatic arthritis, fibromyalgia.

Other Fibrocystic breast disease, fibroadenoma, chronic fatigue syndrome.

ACCESSION NUMBER: 2002:45631 USPATFULL  
TITLE: 1,2-dithiolane derivatives  
INVENTOR(S): Pershadsingh, Harrihar A., Bakersfield, CA, United States  
Avery, Mitchell A., Oxford, MS, United States  
PATENT ASSIGNEE(S): University of Mississippi, University, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6353011	B1	20020305
APPLICATION INFO.:	US 2000-520208		20000307 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-497324, filed on 3 Feb 2000, now patented, Pat. No. US 6204288 Continuation-in-part of Ser. No. US 1999-264370, filed on 8 Mar 1999, now patented, Pat. No. US 6127394		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Gerstl, Robert		
LEGAL REPRESENTATIVE:	Townsend and Townsend and Crew, LLP		
NUMBER OF CLAIMS:	35		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	15 Drawing Figure(s); 15 Drawing Page(s)		
LINE COUNT:	2266		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

DETD . . . adult, (komedonenakne, papulOese, pustulOese, knotige d. h. nodulAere, nodulozystische Akne)  
Z

Akne conglobata, (Sonderform: Hidradenitissupprativa)

Akne fulminans

Akne - Tetrade

Akne neonatorum

Altersakne (M. Favre - Racouchot)

Mechanische Akneformen(Acne excoriee)

Akne cosmetica

Follikulitis bei superinfizierter Akne (Stapylokokken)

berufsbedingte Akneformen (z. B. Chlorakne)

IV. Herpesvirus - Infektionen.

der Gruppe Quercitin, Rutin, Chrysin,

Kaempferol, Myricetin, Rhamnetin, Apigenin, Luteolin, Naringin,

Hesperidin, Naringenin, Hesperitin, Morin, Phloridzin, Diosmin, Fisetin,

Vitexin, Neohesperidin Dihydrochalkon, Flavon, Glucosylrutin und

**Genistein.**

Ascorbylpalmitate, Mg -

Ascorbylphosphate, Ascorbylacetate, Ascorbylglycoside),

Tocotrienole, Tocopherole und deren Derivate (z.B. Vitamin E - acetat,

alpha-, beta-, gamma-, delta-Tocopherole, Tocopherylglycoside), Vitamin

A und Derivate (**Retinol**, Vitamin A - palmitat, Vitamin A -

SAeure) sowie

Konyferylbenzoat des Benzoeharzes, wAessrige oder alkoholische Tabak-,

Tee- undloder Kaffee - Extrakte, Teein, . . .

CLMDE. . . der Gruppe Quercitin, Rutin, Chrysin,

Kaempferol, Myricetin, Rhamnetin, Apigenin, Luteolin, Naringin,

Hesperidin, Naringenin, Hesperitin, Morin, Phloridzin, Diosmin, Fisetin,

Viteyin, Neohesperidin Dihydrochalkon, Flavon, Glucosylrutin und

**Genistein**, alpha-Glucosylrutin, alpha-Glucosylmyricitr in,

alpha-

Glucosylisoquercitrinitrin und alpha-Glucosylquercitrin, alpha-

Glucosylrutin, alpha-Glucosylmyricitrin, alpha-Glucosylisoquercitrinitrin

und alpha-Glucosylquercitrin.

ACCESSION NUMBER: 1996018381 PCTFULL ED 20020514

TITLE (ENGLISH): AGENTS ACTING AGAINST HYPERREACTIVE AND HYPOACTIVE,  
DEFICIENT SKIN CONDITIONS AND MANIFEST DERMATITIDES

TITLE (FRENCH): AGENTS EFFICACES CONTRE DES ETATS CUTANES DEFICIENTS  
HYPER-REACTIFS OU HYPO-ACTIFS ET DES DERMATITES  
MANIFESTES

INVENTOR(S): LANZENDOERFER, Ghita; STAEB, Franz; UNTIEDT, Sven

PATENT ASSIGNEE(S): BEIERSDORF AG; LANZENDOERFER, Ghita; STAEB, Franz;  
UNTIEDT, Sven

LANGUAGE OF PUBL.: German

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9618381	A1	19960620
JP US AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE		
WO 1995-EP4907	A	19951212
DE 1994-P 44 44 238.6		19941213

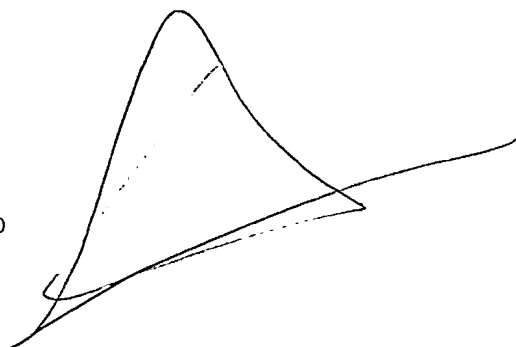
DETD . . . 5,614,201 and U.S. Patent

5,482,710, both to Slavtcheff et al. These mask products

are reported to eliminate pimples, blemishes and the redness of acne. Unfortunately delivery via masks requires the presence of significant amounts of water which may adversely react with moisture sensitive ingredients. Extended drying times. . .

Vitamin A for purposes of this invention include **retinol**, **retinoic acid** as well as retinyl C2\_C22 fatty acid esters.

Ursi (bearberry) 0  
vanilla fruit w  
borage seed oil 0  
wild borage seed oil 0  
Flavanoid Extracts  
hesperedin 0  
neohesperidin w  
quercetin 0  
rutin w  
morin w  
kaempferol 0  
mVricet n w/o  
**genistein** 0  
Phytoestrogen ExtractB  
coumestrol 0  
estriol 0  
phytosterols 0  
Other Extracts  
limonene 0  
ethoxvaunin 0  
chlorogenic acid w  
glutathione w  
hydroquinone 0  
ubiquinone (coenzyme Q) 0  
lipoic acid 0  
N-acetyl cysteine 0  
curcumin 0  
Herbal. . .



ACCESSION NUMBER: 1998042303 PCTFULL ED 20020514  
TITLE (ENGLISH): COSMETIC PRODUCT  
TITLE (FRENCH): PRODUIT COSMETIQUE  
INVENTOR(S): CROTTY, Brian, Andrew; MINER, Philip, Edward; JOHNSON, Anthony, William; ZNAIDEN, Alexander, Paul; COREY, Joseph, Michael; VARGAS, Anthony; MEYERS, Alan, Joel; LANGE, Beth, Anne  
PATENT ASSIGNEE(S): UNILEVER PLC; UNILEVER N.V.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9842303	A1	19981001
DESIGNATED STATES	AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1998-EP1423	A	19980310
PRIORITY INFO.:	US 1997-60/039,378		19970320
	US 1998-60/072,355		19980123

DET D . . . include, for example, dry skin, ichthyosis, palmar and plantar hyperkeratoses, dandruff, lichen simplex chronicus, Darier's disease, keratoses, lentigines, age spots, melasmas, blemished skin, **acne**, psoriasis, eczema, pruritis, inflammatory dermatoses, striae distensae (i.e., stretch marks), warts and calluses.

4,053,630 and 4,363,815, the disclosures of which are all incorporated herein by reference. Suitable therapeutic organic acids may also include derivatives of **retinoic acid**, such as 1-hydroxyretinoic acid and 1-ketoretinoic acid, as described in U.S. Patent No. 4,194,007, the disclosure of which is also incorporated.

The microsphere encapsulated therapeutic organic acid can be readily used in compositions containing other cosmetic and pharmaceutical agents, e.g. anti-fungals, vitamins, sunscreens, **retinoids**, antihistamines, depigmenting agents, anti-inflammatory agents, anesthetics, surfactants, emulsifiers, stabilizers, preservatives, antiseptics, emollients, thickeners, lubricants, humectants, chelating agents, fragrances, colorants and skin penetration enhancers.

The present invention may also include: from about 0.01 wt.% to about 30 wt.%, preferably from about 0.05 wt.% to about 5 wt.%, **retinoids**, such as **retinol**, **retinoic acid**, retinyl palmitate, retinyl propionate or retinyl acetate as well as synthetic **retinoid** mimics; from about 0.001 wt.% to about 10 wt.% hormones such as estriol or estradiol; . . .

quercetin, rutin, daidzein, **genistein**), ferrulic acid derivatives (e.g. ethyl ferrulate, sodium ferrulate) and 6-hydroxy-2,5,7,-tetramethyl-chroman carboxylic acid. The compositions may also contain effective concentrations of water-soluble antioxidants, . . .

CLAIMS. . . 3, wherein said composition further comprises at least one additional agent selected from the group consisting of antifungals, vitamins, sunscreens, keratolytic agents, **retinoids**, antiallergenic agents, depigmenting agents, anti-inflammatory agents, anesthetics, surfactants, moisturizers, exfoliants, emulsifiers, antioxidants, insect repellents, sunscreen agents, stabilizers, preservatives, antiseptics, emollients, thickeners, lubricants, humectants, chelating. . .

ACCESSION NUMBER: 1999055307 PCTFULL ED 20020515  
TITLE (ENGLISH): METHOD OF TREATING THE SKIN WITH ORGANIC ACIDS IN ANHYDROUS POLYMERIC DELIVERY SYSTEMS  
TITLE (FRENCH): PROCEDURE DE TRAITEMENT DE LA PEAU PAR DES ACIDES ORGANIQUES DANS DES SYSTEMES D'ADMINISTRATION POLYMERES ANHYDRES  
INVENTOR(S): CURTIS, Ernest, S.; KALAFSKY, Robert; KAPLAN, Elinor, R.  
PATENT ASSIGNEE(S): AVON PRODUCTS, INC.

LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9955307	A1	19991104
DESIGNATED STATES	AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1999-US7473	A	19990405
PRIORITY INFO.:	US 1998-09/069,089		19980428

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ABEN . . . on human skin (i.e., chronological aging of human skin) can be prevented and treated with the topical application of a **retinoid**, preferably

**retinol**. We have found that some of the same pathways (namely the stress-activated pathways, SAPs) activated in photoaging of human skin. . . that other pathways (namely the mitogen-activated ERK pathway) is depressed in the same skin. Treatment of chronologically-aged skin with a **retinoid** both inhibits degradation of dermal collagen and promotes procollagen synthesis.

Biopsied sections from skin of elderly (80+ years old) show. . .  
ABFR . . . du temps sur la peau humaine (c. -a-d. le vieillissement de la peau humaine du a l'age) par l'application topique d'un **retinoide**, de preference du **retinol**. Il a ete decouvert que certaines voies (a savoir les voies activees par le stress, SAP) activees au cours du. . . voie ERK activee par mitogenes) sont faibles dans ladite peau. Le traitement de peau de personnes agees a l'aide d'un **retinoide** permet d'inhiber la degradation de collagene dermique et de favoriser la synthese de procollagene. Des coupes de biopsies de peau. . .

DETD This invention relates to methods and compositions, especially those comprising

**retinoids**, preferably topically applied, which are useful for improving keratinocyte and fibroblast proliferation, decreasing matrix metalloproteinase (MMP) expression, and improving collagen synthesis in. . .

EP-A2-0 379,367 describe a method for the treatment or prevention of intrinsically aged skin with retinoids. Kligman et al. tested all trans-

**retinoic acid** (as Retin-A' cream) on albino hairless mice and on 5 elderly caucasian respectively; see also U.S. Pat. No. 3,060,229. Retinal. . . wrinkles, warts, psoriasis, eczema, dandruff, and the like (see EP-A2-0 391 033). There is also

'dence to indicate that tretinoin (all trans **retinoic acid**) improves the appearance of

evi I I 1

photoaged skin. Albert M. Kligman, Current Status of Topical Tretinoin in the

Treatment of. . .

naringenin and/or quereetin, and a retinoid. The compositions are described as useful for treating many unrelated skin conditions, such as wrinkles, **acne**, skin lightening, and age spots. The action of their composition on human skin is described with respect to an enzyme (transglutaminase) important. . .

promote procollagen synthesis, the application preferably being performed on a regular basis. A preferred class of compounds that perform both functions are **retinoids**, especially **retinol** and all **trans-retinoic acid**.

procollagen levels can be increased in aged human skin by the preferably regular application to the skin of effective amounts of a

**retinoid**; in preferred embodiments, the treatment also includes inhibition of collagen degradation by the use of an MMP inhibitor.

and fibroblasts, each beneficial to the integrity of the skin, are each increased in number by the topical application of a **retinoid**, again applied preferably on a regular basis. Fibroblasts are trophic to the epidermis; under normal conditions they secrete a number of growth. . .

in the skin, and increasing ERK activity, both in aged skin, by the topical application of an effective amount of a **retinoid** to the aged skin.

epidermal thickness (II Q, and keratinocyte density (II D) in elderly (80+ years old) skin upon application of a retinoid (1% **retinol** ; one application, occluded, and examined seven days later).

5

Fig. 12 depicts the effect of **retinoid (retinol)** treatment on the growth of human keratinocytes and fibroblasts cells cultured ex vivo from biopsy samples.

13B), an elderly individual (13C and 13D), and the same elderly individual (13E and 13F) after a single application of 1% **retinol** (occluded, left for seven days, then biopsied).

effect on activities of three MMP enzymes (MMPs 1, 2, and 9; analogous to Fig. 4) after a single application of **retinol** to elderly skin as determined by biopsy.

Fig. 15 depicts the **retinoic acid**-mediated induction of Type I collagen synthesis in cultured human skin fibroblasts.

Fig. 16 depicts the in vivo induction of Type III procollagen al(III) mRNA caused by **retinol** administration to elderly skin.

Fig. 17 depicts the in vivo induction ERK activity caused by

## **retinol**

administration to elderly skin.

18 is a photomicrograph showing in stained sectioned biopsies of elderly skin

that, seven days after a single application of 1% **retinol**, c-Jun protein is decreased and the amounts of Types I and III procollagen in the skin are increased.

Our invention is generally directed to the topical administration, preferably on a regular basis, of an amount of a retinoid, preferably **retinol** or **retinoic acid**, to the skin of an elderly person in amounts effective to induce the proliferation of at least one of keratinocytes and.

of chronologically-aged skin, 17 subjects having an age of at least 80 years old were given one topical treatment with 1% **retinol** or with vehicle alone, the test area was occluded for seven days, and the test area was then biopsied. The vehicle was. . . reference to Fig. 2, namely the number of fibroblasts and keratinocytes, the epidermal thickness, and undesirable dermal connective tissue features. In comparing **retinol**-treated skin with vehicle-treated skin from the same individuals, as shown in Fig. 11, there were increased numbers of keratinocytes (I IA) and fibroblasts (I ID) per section in the **retinol**-treated skin (273% ( $p < 0.001$ ) and 30% ( $p < 0.05$ ) mean increases, respectively). In addition, I id treatment increased the epidermal thickness substantially (II Q). Due to the **retinol** I I short duration of the retinoid (**retinol**) treatment, little change in the number of detrimental dermal connective tissue features (II B) was apparent.

Figs. 12A and 12B demonstrate the effects of 7-day in vivo **retinol** treatment on ex vivo growth of keratinocytes and fibroblasts extracted from biopsies of sun-protected skin taken from our individual volunteers over age 80. That is, an elderly 15 volunteer was treated with **retinol** (one application of 1% **retinol**, occluded for seven days), the treated area was biopsied, and the keratinocytes and fibroblasts from the biopsy were cultured ex vivo. This **retinol** treatment of the cells in vivo resulted in a substantial increase in the ex vivo growth of both cell types. In. . . 30% (12A) while fibroblast growth increased by about 200% (12B), with  $p < 0.05$  for both. Accordingly, the topical application of a **retinoid** to aged skin would be expected to increase the number of keratinocytes and/or the number of fibroblasts in the skin.

Figs. 13E and 13F depict **retinol**-treated, sun-protected skin from the same individual from whom the biopsy shown in Figs. 13C and 13D was taken, after 7 days

having been treated as described previously (one application of **retinol**). The changes to the skin shown are quite remarkable and unexpected. The epidermis thickened, the interfacial surface area increased as evidenced by.

Fig. 14C depict the average MMP activity levels (for collagenase MMP-I and gelatinases MMP-9 and MMP-2, respectively) after treatment of elderly individuals with **retinol**. As shown in Fig. 14, seven days after a single **retinol** treatment, the activities of MMP-I and MMP-9 were both decreased (48% and 39% decreases, respectively, with  $p < 0.001$  for both). From seven volunteers over 80 years old and cultured fibroblasts from biopsy samples of their unexposed (sun-protected) skin, we found that a **retinoic acid** concentration of 0.25  $\mu\text{g}/\text{ml}$  increased the relative expression of collagen three fold from that of untreated cells, and 0.5 and 1.0.

Seven 80+ year old individuals were treated clinically with 1% **retinol** cream, applied once to sun-protected skin, covered with a patch, and left undisturbed for seven days. Biopsies of these treated areas under.

Using the same technique as previously described for **retinoid** treatment (1% **retinol** applied to sun-protected skin, occluded, and examined seven days later), we treated and then tested three of our 80+ year old volunteers to determine the effect of **retinoid** treatment on ERK activity. The results of biopsies from these individuals show that after the treatment ERK activity in vivo was.

MMP formation and is formed by the heterodimerization of c-Jun and c-Fos proteins. Fig. 18A shows that after one week of **retinoid** (**retinol**, ROL) treatment, the c-Jun level in elderly skin (c-Jun being stained red) is significantly reduced (almost absent) when compared with a biopsied. dermis in Fig. 18C is an artifact of the section made; there is clearly a higher level of staining in the **retinol** treated section than in the vehicle treated section.) Accordingly, in one embodiment the invention comprises a method of rejuvenating aged skin by the.

Preferred treatment and maintenance regimes use an effective amount of about 0.4% **retinol**, although higher doses can be used where warranted. **Retinol** is the preferred **retinol** I I 'd.

**retinol**  
In another embodiment, the invention provides a method of inducing in



vivo  
keratinocyte and/or fibroblast proliferation by the topical  
administration of an effective,  
non-toxic amount of a retinoid (preferably **retinol** or all  
trans **retinoic acid**) for an  
effective period of time. Again, treatment is preferably daily, once or  
twice, with the  
amount of retinoid preferably being. . .

the topical administration of an effective amount  
of a retinoid for an effective period of time; again the preferred  
retinoids are **retinoid**  
and all trans **retinoic acid**. Again, treatment is preferably  
daily, once or twice, with the  
amount of retinoid preferably being about 0.1%, to about 1.0%.

reduced cell growth that results, ultimately, in aged skin. Our results  
shown in  
Figs. 15-17 prove the in vivo effectiveness of **retinoid**  
treatment in increasing the  
activity level of ERK and the production Types' I and III procollagen .

the face and hands. Taken with the teachings of the  
aforementioned patent and provisional applications directed to  
photoaging, daily  
application of a **retinoid** to the skin will ameliorate the  
effects of natural aging as well  
as the sun's exacerbating effects on natural aging of. . .

decreased amounts of c-Jun,  
and increased amounts of Types I and/or III procollagen. Using the same  
technique  
described for retinoid treatment (1% **retinol** applied to  
sun-protected skin, occluded,  
and examined seven days later), we tested three of our 80+ year old  
volunteers. The  
results of. . .

which  
MMPs are produced naturally. Aspirin and E5510 (described by Fujimori,  
T., et al.,  
Jpn J Pharmacol (1991) 55(1):81-91) inhibit NF-KB activation.  
**Retinoids** such as those  
disclosed in U.S. Pat. No. 4,877,805 and the dissociating retinoids that  
are specific for  
AP-1 antagonism (such as those. . . Enhancing the Therapeutic Use of  
1,25(OH)2D3), filed April 4, 1997, the  
disclosure of which is incorporated herein by reference. Other  
retinoids, besides

**retinol**, include natural and synthetic analogs of vitamin A (  
**retinol**), vitamin A  
aldehyde (retinal), vitamin A acid (**retinoic acid** (RA)),  
including all-trans, 9-cis, and

16  
-cis **retinoic acid**), etretinate, and others as described in  
EP-A2-0 379367,  
US 4,887,805, and US 4,888,342 (the disclosures of which are all  
incorporated herein  
by reference). Various synthetic **retinoids** and compounds  
having **retinoid** activity are  
expected to be useful in this invention, to the extent that they exhibit  
**retinoid** activity  
in vivo, and such are described in various patents assigned on their  
face to Allergan

Inc., such as in the following. . . 5,677,451; 5,677,323; 5,677,320; 5,675,033; 5,675,024; 5,672,710; 5,688,175; 5,663,367; 5,663,357; 5,663,347; 5,648,514; 5,648,503; 5,618,943; 5,618,931; 5,618,836; 5,605,915; 5,602,130. Still other compounds described as having **retinoid** activity are described in other U.S. Patents, numbered.

558648 (disclosed therein as useful for inhibiting MMI's in the treatment of, among other etiologies, skin ulcers, skin cancer, and epidermolysis bullosa). **Retinoids** have been reported by Goldsmith, L.A. (Physiology, Biochemistry, and Molecular Biology of the Skin, 2nd.

of possible allergic or sensitization reactions, the topical administration of tetracyclines should be monitored carefully for such untoward reactions. Other MMP inhibitors include

**genistein** and **quercetin** (as described in US 5637703, US 5665367, and FR-A-2,671,724, the disclosures of which are incorporated herein by reference) and related. . .

to provide preferably about 5 @Lg/CM<sup>2</sup> skin when applied. For example, a preferred composition for use in this invention is Retin-A' **retinoic** acid gel and cream (available from Ortho Pharmaceuticals for the treatment of **acne vulgaris**), in strengths of from 0.01% to 0.1%; the vehicle preferably includes, depending upon the particular formulation, at least one of butylated. . .

in young individuals (such as those aged 40 and younger). In particular, we have found that a single application of 1% **retinol** to chronologically-aged skin, covered with an air-permeable adhesive bandage, and examined seven days later, resulted in procollagen protein levels comparable to. . . in sun-protected skin of significantly younger individuals (e.g., under age 40). It would be more

18 preferable for elderly persons to apply the **retinoid** once or twice daily to maintain -a therapeutic regimen, although the agent could be applied on a less frequent but preferably regular. . .

and so treatment of elderly skin with both a 'd and an MMP inhibitor is important for achieving the desired benefits of

**retinol** I I I I I improved procollagen blosynthesis. In fact, we have found in skin not having a reduced level of collagen,. . .

Although **retinol** is the preferred compound for topical administration, effective derivatives of **retinol** that would be expected to be useful for

practicing this invention include retinal, **retinoic** acid (including all trans, 9-cis, and 13-cis isomers) and derivatives thereof (such as 7,8-didehydroretinoic acid), and others as described by Kligman et. . .

skin samples by guanidinium hydrochloride lysis and ultracentrifugation (as described by G.J. Fisher et al., Cellular, immunologic and biochemical characterization of topical **retinoic** acid-treated human skin, J Investig. Dermatol, 96:699-707 (1991)). Northern analysis of total RNA (40 @ig/lane) with randomly 12p primed labelled cDNA probes for the particular mRNA to be determined were performed as described by G.J. Fisher et al (in All ttvns **retinoic** acid induces cellular **retinol**-binding protein in human skin in vivo, J Investig. Dermatol, 105:80-86 (1995)). Type III procollagen rnRNA was determined usincy reverse transcriptase polymerase chain. . .

nuclear extracts from human skin by Western analysis as described by G.J. Fisher et al. (in Immunological identification and functional quantitation of **retinoic** acid and **retinoid** X receptor proteins in human skin, J Biol.

CLMEN 3 The method of claim 2, wherein the rennold is selected from **retinol**, retinal, **retinoic** acid, a **retinoic** acid salt, a derivative or analog thereof, or a mixture thereof

4 The method of claim 3, wherein the retinold is **retinol** 'd. I or **retinoic** aci

9 A method of preventing chronologically-aged skin, comprising providing a topically administerable, non-toxic amount of a **retinoid** in a cosmetically suitable vehicle and applying said **retinoid** to the skin at least once weekly in an amount effective to no rmalize procollagen synthesis and inhibit colla en degradation.

9

I. . . claim 9, wherein the skin is sun-protected skin.

I 11. The method of claim 9, wherein the retinold is selected from **retinol**, retinal, **retinoic** acid, a **retinoic** acid salt, a derivative or analog thereof, or a mixture thereof

12 The method of claim I 1, wherein the retinold is **retinol**.

13 The method of claim 9, wherein the **retinoid** is applied daily.

normalizing the production of procollagen in chronologically--aged skin, comprising the steps of providing a topically administerable, non-toxic

retinold and administering said **retinoid** to the skin in an amount effective to normalize the production of procollagen.

15 The method of claim 14, wherein the retinold is **retinol**.

17 The method of claim 16, wherein the **retinoid** is applied daily.

24

. The method of claim 14, further comprising the step of simultaneously inhibiting the degradation of collagen, said method. . .

the activity level of ERK in aged human skin which comprises the topical application of an effective, non-toxic amount of a **retinoid** to said skin.

23 The method of claim 22, wherein the retinold is retinold or **retinoic acid**.

25 The method of claim 22, wherein the **retinoid** is **retinol** d or **retinoic acid**.

25

ACCESSION NUMBER: 1998036742 PCTFULL ED 20020514  
TITLE (ENGLISH): METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING CHRONOLOGICAL AGING IN HUMAN SKIN  
TITLE (FRENCH): PROCEDES ET COMPOSITIONS SERVANT A PREVENIR ET A TRAITER UN VIELLISSEMENT DE LA PEAU HUMAINE DU A L'AGE  
INVENTOR(S): VARANI, James; FISHER, Gary, J.; VOORHEES, John, J.; KANG, Sewon  
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF MICHIGAN  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9836742	A1	19980827
DESIGNATED STATES	AU BB BG BR CA CN CU CZ <del>EE</del> HU ID IL IS JP KR LC LT LV MK MN MW MX NO NZ PL RO SG SK SL TR TT UA UG VN GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1998-US3743	A	19980223
PRIORITY INFO.:	US 1997-60/040,594		19970225
	US 1997-60/042,976		19970407

L48 ANSWER 8 OF 45 PCTFULL COPYRIGHT 2002 Univentio  
ABEN . . . synthesis of procollagen. This UV-induced inhibition of the synthesis of collagen can be prevented by the topical application of a **retinoid** or c-JUN inhibitor to the skin prior to its exposure to UV radiation.  
ABFR . . . synthese de procollagene. On peut empecher cette inhibition induite par UV de la synthese du collagene par l'application topique d'un **retinoide** ou d'un inhibiteur de c-JUN sur la peau avant son exposition a un rayonnement UV.  
DETD **Retinoids** have been used to retard the effects of photoaging in skin appearing to have been damaged by exposure to the sun. . . .  
of photoaged skin after photoaging has become apparent clinically. This patent indicates there is little point in

beginning the application of a **retinoid** to treat photodamaged skin until the effects of photoaging begin to appear.

then secreted from the cell upon demand, collagen is secreted continuously. According to Goldsmith, op. cit. (at 492), not only do **retinoic** acid, glucocorticoids, and vitamin D3 derivatives all decrease collagen synthesis, but so do other **retinoids**.

In light of these findings, our invention generally can be summarized as the topical administration of a **retinoid** in an amount effective to reduce the inhibition of collagen synthesis mediated by exposure to UV radiation by applying the **retinoid** to the skin at least about 16 hours prior to exposure.

Figs. 10A-10D depict cross-sections of biopsies of human skin treated with either **retinoic** acid or a vehicle alone and stained for the expression of Type I procollagen mRNA, both before and after exposure of.

Type I procollagen protein in human skin after treatment with **retinoic** acid or a vehicle alone, both before and after exposure of the treated skin to UV radiation, and which shows the protective effect of **retinoids** on procollagen protein synthesis.

Type I procollagen precursor protein in human skin both before and after exposure to UV radiation where the exposed skin had been treated previously with **retinoic** acid or a vehicle alone.

Figs. 13A-13D depict cross-sections of biopsies of human skin treated with either **retinoic** acid or a vehicle alone and stained for the expression of Type III procollagen mRNA, both before and after exposure of.

Figs. 14A-14D depict cross-sections of biopsies of human skin treated with either **retinoic** acid or a vehicle alone and stained for the expression of Type III procollagen protein, both before and after exposure of.

Type III procollagen protein and the pN precursor protein in human skin in vivo where the skin was pretreated with either **retinoic** acid or a vehicle alone and then exposed to UV radiation.

depicting our results of the assayed amount of soluble collagen (measured via hydroxyproline content) in human skin in vivo treated with either **retinoic** acid or a vehicle alone, both before and after exposure to UV radiation.

#### Retinoid Pretreatment

We tested whether retinoids, in particular all-trans **retinoic** acid, would have any effect on the loss of procollagen mRNA and/or the procollagen

proteins in human skin after exposure to UV radiation. (Unless otherwise noted, the **retinoic** acid used in the experiments described herein was all-trans.) Separate areas of skin from each of our volunteers were treated with.

The site of the volunteers' skin to be exposed to UV radiation was treated prior to UV exposure with either the all-trans **retinoic** acid or the control vehicle. Pretreatment times of eight hours before exposure did not appear to significantly prevent reduction in collagen synthesis, . . . we describe below (in which a reduction in collagen biosynthesis was prevented). Nevertheless, it should be understood that a period of pretreatment with **retinoid** more than eight and less than twenty-four hours before UV exposure may likely be sufficient to prevent the reduction in collagen biosynthesis we have observed. Furthermore, it should be understood that in all of the following examples treatment with a **retinoid** (e.g., **retinoic** acid-treated) or the vehicle (e.g., vehicle-treated) should each be understood as pretreatment 24 hours before UV exposure.

Our invention on the use of **retinoids** to protect against the UV-Induced loss of procollagen Types I and III is more graphically depicted in Fig. 10, which shows stained biopsy cross-sections (analogous to those shown in Fig. 1) of vehicle- and **retinoid**-treated skin prior to UV exposure, and then after UV exposure. Figure 10 shows cross-sections stained for Type I procollagen mRNA (the dermis-epidermis Junction has been delineated electronically with a solid line). Fig. 10A is vehicle-treated skin and Fig. 10B is all-trans **retinoic** acid-treated skin, both prior to UV exposure. In this pair of photographs, the procollagen mRNA is expressed in the various fibroblasts in the dermis; while the **retinoic** acid-treated (RA caption in the figure) skin shows darker staining, the number and density of the fibroblasts producing the mRNA for.

signalling necessary for procollagen biosynthesis, as shown in Fig. 10D. Comparing Figs. 10C and 10D, it is striking to note that the **retinoid**-treated skin appears unaffected by exposure to UV radiation, to the extent that Type I procollagen mRNA is expressed to the same degree.

and II B. Biopsies taken 24 hours after exposure to UV radiation of 2MED yield striking differences between the control and the **retinoid** treated areas. Fig. 10C shows the control (vehicle-treated) skin biopsy in which the staining at the dermis-epidermis junction is

significantly. . .

is a histogram depicting our results of Western blot analyses of biopsies from our volunteers where the skin was pretreated with **retinoic** acid or the vehicle alone, biopsied, exposed to UV radiation, and biopsied again. As shown, prior to UV exposure the vehicle-treated area. . . has an amount of Type I procollagen and the pN collagen precursor that have been normalized to a value of 1. Unexposed **retinoic** acid-treated skin had essentially the same amounts of Type I procollagen and the pN precursor protein. The biopsies of UV-exposed skin. . . I procollagen protein and pN collagen precursor protein than were present before exposure. These results are consistent with those discussed previously. The **retinoic** acid-treated areas, though, showed very little loss of both the Type I procollagen and the pN collagen precursor protein; both values were. . .

The use of **retinoids** to protect against the UV-Induced loss of Type III procollagen is also graphically depicted in Fig. 13, which shows biopsied cross-sections. . . Type III procollagen mRNA is expressed in fibroblasts in the dermis, prior to UV exposure, in both vehicle-treated (Fig. 13A) and **retinoic** acid-treated (Fig. 13B) skin. After exposure to UV radiation, the vehicle-treated skin showed essentially a complete absence of the expression of the Type III procollagen mRNA (Fig. 13C), whereas the **retinoid**-treated skin showed little, if any, reduction in the expression of Type III procollagen mRNA (Fig. 13D).

of the Type III procollagen protein and the pN collagen precursor protein (analogous to Fig. 12) in human skin treated with either **retinoic** acid or vehicle alone prior to exposure, and biopsied both before and after UV exposure. Again, prior to UV exposure both vehicle (VEH) and **retinoic** acid (RA) treated skin had essentially the same amounts of these proteins. After 2 MEDs of UV exposure, the amounts of these proteins in the skin had been essentially halved, as shown by the VEH+UV bars. However, the **retinoic** acid-treated UV-Irradiated sections (RA+UV) had essentially the same amounts of these proteins as both the control and the **retinoic** acid-treated areas prior to exposure.

of the volunteers' skin to be treated with a **retinol** id prior to UV exposure was pretreated 24 hours prior to exposure. We pretreated certain volunteer's sun-protected skin with 0.1% all **trans retinoic** acid 8 hours prior to exposure to 2 MEDs of UV radiation. As shown in Fig. 17, the

level of soluble collagen. . . UV exposure where the exposed skin had been pretreated with a retinoid 8 hours before exposure was essentially the same in the retinoid-treated and the control (vehicle-treated) skin. Thus, as mentioned above, to prevent UV-Induced loss of collagen synthesis using a retinoid, pretreatment 24 hours. . .

inhibition of collagen synthesis. These data indicate that c-JUN mediates inhibition of type I procollagen gene expression by UV radiation. Accordingly, agents, like retinoids, that block induction of c-JUN by UV radiation would be effective in protecting skin exposed to UV from loss of procollagen.. . .

Retinoids useful in practicing the present invention include those such as disclosed in U.S. Pat. No. 4,877,805 and the dissociating retinoids that are described by Fanjul et al. in Nature (1994) 372:104-110. Retinoids typically include natural and synthetic analogs of vitamin A (retinol), vitamin A aldehyde (retinal), vitamin A acid (retinoic acid (RA)), including all-trans, 9-cis, and 13-cis retinoic acid, tretinate, and others as described in EP-A2-0 379367, US 4,887,805, and US 4,888,342 (the disclosures of which are all incorporated herein by reference). Various synthetic retinoids and compounds having retinoid activity are expected to be useful in this invention, to the extent that they exhibit activity in vivo, and such are described in various assigned on retinol I I I I patents I their face to Allergan Inc., such as in the following U.S. Patents, numbered.

the like. The disclosures of all of the foregoing and following patents and literature references are hereby incorporated herein by reference. While retinol is the preferred compound for topical administration, effective derivatives of retinol that would be expected to be useful for practicing this invention specifically include retinal, and (including all-trans, 9-cis, and 13-cis isomers) and derivatives retinoic acid I I I I thereof (such as 7,8-didehydroretinoic acid), and others as described by Kligman et al., the disclosure of which. . . @.ig &plusmn; 2.5 gg/CM<sup>2</sup> skin when applied. For example, a preferred composition for use in this invention is Retin-A' retinoic acid gel and cream (available from Ortho Pharmaceuticals) available presently for the treatment of acne vulgaris, in strengths of from 0.01% to 0.1%; the vehicle preferably includes, depending upon the particular formulation, at least one of butylated. . .



receptors (such as suramin, also known as an antiprotozoal), 7 and antagonists of epidermal growth factor receptors (such as: AG , Erbstatin analog; **Genistein**; Lavendustin A; Tyrphostins 1, 9, 23, 25, 46, 47, and 51- and I'D 153035).

(e.g., ascorbyl glucoseamine), glutathione, and NAC; and (111) other compounds such as one of the pigments that makes tomatoes red, lipoic acid, **genistein**, and ebselen and other selenium compounds. Glutathione and its precursors, such as N-acetyl cysteine (NAQ, more broadly N-CH<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>, Co cysteine (wherein n is . . .

skin samples by guanidinium hydrochloride lysis and ultracentrifugation (as described by G.J. Fisher et al., Cellular, immunologic and biochemical characterization of topical **retinoic** acid-treated human skin, J Investig. Dermatol, 96:699-707 (1991)). Northern analysis of total RNA (40 gg/lane) with randomly primed 12p labelled cDNA probes for the particular mRNA to be determined were performed as described by G.J. Fisher et al. (in All trans **retinoic** acid induces cellular **retinol** -binding protein in human skin in vivo, J Investig. Dermatol, 105:80-86 (1995)). Type III procollagen mRNA was determined using reverse transcriptase polymerase chain. . .

were detected in skin extracts by Western analysis as described by G.J. Fisher et al. (in Immunological identification and functional quantitation of **retinoic** acid and **retinoid** X receptor proteins in human skin, J Biol. Chem., 269- 20635 (1994)).

CLMEN 2 The method of claim 1, wherein the retinoid is all-trans **retinoic** acid, **retinol**, or a mixture thereof.

27 The method of claim 26, wherein the antagonist is suramin, AG-494, Erbstatin analog, **Genistein**, Lavendustin A, Tyrphostins 1, 9, 23, 25,

reduction in collagen biosynthesis in human skin mediated by exposure of the skin to UV radiation, comprising an effective amount of a **retinoid** and a pharmaceutically acceptable carrier therefor, provided that said composition is applied to the skin prior to its exposure to UV radiation.

29 The composition of claim 28, wherein the retinoid is all-trans **retinol**, or a mixture thereof. **retinoic** acid

40 The method of claim 39, wherein the antagonist is suramin, AG-494, Erbstatin analog, **Genistein**, Lavendustin A, Tyrphostins 1, 9, 23, 25,

ACCESSION NUMBER: 1999051220 PCTFULL ED 20020515  
TITLE (ENGLISH): METHODS AND COMPOSITIONS FOR REDUCING UV-INDUCED INHIBITION OF COLLAGEN SYNTHESIS IN HUMAN SKIN  
TITLE (FRENCH): PROCEDES ET COMPOSITIONS DE REDUCTION DE L'INHIBITION DE LA SYNTHESE DE COLLAGENE INDUITE PAR UN RAYONNEMENT

INVENTOR(S) : UV DANS LA PEAU HUMAINE  
 PATENT ASSIGNEE(S) : FISHER, Gary, J.; VOORHEES, John, J.  
 LANGUAGE OF PUBL.: THE REGENTS OF THE UNIVERSITY OF MICHIGAN  
 DOCUMENT TYPE: English  
 PATENT INFORMATION: Patent

	NUMBER	KIND	DATE
	WO 9951220	A1	19991014
DESIGNATED STATES	AL AU BA BB BG BR CA CN CU CZ EE GD HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA UZ VN YU ZA GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1999-US7267	A	19990402
PRIORITY INFO.:	US 1998-60/080,437		19980402

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DETD . . . to changes  
 in gene expression is poorly understood. Full activation of PPARGgamma  
 and/or  
 PPARalpha and/or PPARDelta requires its functional dimerization with the  
**retinoid X**  
 receptor (RXR) to form PPARGgamma/RXR or PPARalpha/RXR or PPARDelta/RXR.  
 The  
 endogenous ligand for RXR is 9-cis-**retinoic** acid. Nutrient  
**retinoids** and **retinoic** acid  
 such as 13-all-trans-**retinoic** acid are converted to 9-cis-, 1  
 1 -cis-, or 13-cis-**retinoic** acid  
 by ubiquitous intracellular isomerases (Warrell Jr et al, New Engl. J.  
 Med. 329(3):177-  
 189 (1993)).- The full spectrum of genes that. . .

PPARGamrna, or PPARalpha, or PPARDelta, or co-activators of aijy of  
 these  
 subtypes are: inflammatory skin diseases (e.g. psoriasis, atopic,  
 dermatitis, eczema, **acne**  
 vulgaris, and other den-natitides), neurodegenerative diseases (e.g.  
 multiple sclerosis,  
 Alzheimer's disease, Parkinson's disease), cardiovascular diseases (e.g.  
 atherosclerosis,  
 venous and arterial occlusive diseases, restenosis. . .

either as a  
 single agent, or in combination with a natural or synthetic compounds.  
 Such compounds  
 include agonists for PPARalpha, PPARDelta, PPARGgamma, **retinoid**  
 X receptor (RXR),  
 vitamin D receptor (VDR), glucocorticoid receptor (GR), Liver X receptor  
 (LXR) or  
 LXR/RXR (e.g. an oxysterol (22(R)-hydroxycholesterol,  
 25-hydroxycholesterol, 7a-  
 hydroxycholesterol,. . .

[00571 Other nuclear receptors to which the present invention applies  
 are: the  
 constitutive androstane (xenobiotic) receptor (CAR), the  
**retinoid X** receptor (RXR), the  
 pregnane X receptor, the Farnesiod X receptor, the liver X receptor, and  
 the steroid X  
 receptot These nuclear. . .

[01881 The compounds can be used to treat inflammatory, proliferative or degenerative skin disease, such as psoriasis, keratitis, hidradenitis, ichthyosis, **acne** vulgaris, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic dermatitis, chemical (irritant) dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, seborrheic. . .

second

agent selected from the above-identified categories of compounds, administered orally, topically or intravenously. A preferred dosage range for administration of a **retinoic acid** derivative or **retinoid** would typically be from 0.1 to 100 mg per square-meter of body surface area, depending on the drug's ability. . . times per day. For synergistic therapy, the preferred dosages and routes and frequency of administration of the vitamin D analogs or **retinoid** compounds can be similar to the dosages and routes and frequency of administration ordinarily recommended for these agents when given without PPARgamma activators. Examples of

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effective **retinoids** are 9-cis-**retinoic acid**, 13-cis-**retinoic acid**, all-trans-**retinoic acid** (at-RA). Preferred **retinoids** for this purpose would include 13-cis-**retinoic acid**, tazarotene, or Targretin. A preferred dosage range for systemic administration of a vitamin D analog or **retinoid** derivatives are the same as those described elsewhere in this disclosure.

the tocopherols (e.g. vitamin E, vitamin E succinate), carotenes and carotenoids (e.g. beta-carotene), alpha-lipoic acid, probucols, flavones, isoflavones and flavonols (e.g. quercetin, **genistein**, catechin, apigenin, lutein, luteolin), glutathione and its derivatives (e.g. N-acetylcysteine and dithiothreitol), and phytoestrogens and phenolic anthocyanidin and procyanidin derivatives (e.g. resveratrol, cyanidin, . . .

Derivative - A Clinical Trial

[0267] The PPAR-mediated disease is an inflammatory, proliferative or degenerative skin disease such as psoriasis, keratitis, hidradenitis, ichthyosis, **acne**, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic dermatitis, chemical (irritant) dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, seborrheic keratosis, . . .

universalis)

**Acne** (all forms, including a. vulgaris, a. rosacea, a. inversa, cystic **acne**).

ACCESSION NUMBER: 2002076177 PCTFULL ED 20021011 EW 200240  
TITLE (ENGLISH): DESIGN AND SYNTHESIS OF OPTIMIZED LIGANDS FOR PPAR  
TITLE (FRENCH): CONCEPTION ET SYNTHÈSE DE LIGANDS OPTIMISÉS POUR PPAR  
INVENTOR(S): PERSHADSINGH, Harrihar, Ajodhya; AVERY, Mitchell, Allen

PATENT ASSIGNEE(S): BETHESDA PHARMACEUTICALS, INC., for all designates  
 States except US; PERSHADSINGH, Harrihar, Ajodhya, for  
 US only; AVERY, Mitchell, Allen, for US only  
 AGENT: JOHNSTON, Madeline, I.  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2002076177	A2	20021003
DESIGNATED STATES	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2002-US9287	A	20020325
PRIORITY INFO.:	US 2001-60/278,097		20010323
	US 2001-60/283,774		20010413

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DETD Anti-Acne Actives.

Examples of useful anti-acne actives include the keratolytics  
 such as salicylic acid  
 (o-hydroxybenzoic acid), derivatives of salicylic acid such as  
 5-octanoyl salicylic acid and  
 4-methoxysalicylic acid, and resorcinol; **retinoids** such as  
**retinoic** acid and its derivatives  
 (e.g., cis and trans); sulfur-containing D and L amino acids and their  
 derivatives and salts,  
 particularly their N-acetyl. . .

Examples of antiwrinkle and anti-skin atrophy actives include  
**retinoic** acid and its  
 derivatives (e.g., cis and trans); **retinol**; retinal; retinyl  
 esters (e.g., retinyl acetate, retinyl  
 palmitate, and retinyl proprionate); vitamine B3 compounds (such as  
 niacinamide and  
 nicotinic acid), salicylic acid. . . (available  
 from Laboratories Serobiologiques); formononetin; forsythia fruit  
 extract; gallic acid  
 esters; gamma butyric acid; GATULINE RC (available from Gattlefosse,  
 located in Priest,  
 France); **genistein**; genisteine; genistic acid; ginkgo bilboa  
 extracts; ginseng extracts;  
 ginsenoside (R0, R6-1, R6-2, R6-3, RC, RD, RE, RF, RF-2, RG-1, RG-2);  
 gluco pyranosyl-  
 I-ascorbate;. . .

phosphate, MELAWHITE (available from Pentapharm),  
 morus alba extract, mulberry root extract, niacinamide, 5-octanoyl  
 salicylic acid, parsley  
 extract, phellinus linteus extract, pyrogallol derivatives,  
**retinoic** acid, **retinol**, retinyl esters  
 (acetate, propionate, palmitate, linoleate), 2, 4 resorcinol  
 derivatives, 3, 5 resorcinol  
 derivatives, rose fruit extract, salicylic acid, Song-Yi extract, 3, . .

the group  
 consisting of salicylic acid, benzoyl peroxide, 3-hydroxy benzoic acid,  
 glycolic acid, lactic  
 acid, 4-hydroxy benzoic acid, acetyl salicylic acid, niacinamide, cis-  
**retinoic acid**, trans-  
**retinoic acid**, **retinol**, retinyl palmitate,  
 2-hydroxybutanoic acid, 2-hydroxypentanoic acid,  
 2-hydroxyhexanoic acid, cis-**retinoic acid**, trans-  
**retinoic acid**, **retinol**, phytic acid, N-acetyl-  
 L-cysteine, lipoic acid, azelaic acid, arachidonic acid,  
 benzoylperoxide, tetracycline,  
 ibuprofen, naproxen, hydrocortisone, acetaminophen, resorcinol,  
 phenoxyethanol,  
 phenoxypropanol, phenoxyisopropanol, 2,4,4'-trichloro-2'-hydroxy  
 diphenyl ether, . . .

CLMEN. . . said cleansing article further  
 comprises a safe and effective amount of one or more active ingredients  
 selected from the group  
 consisting of anti-**acne** actives, anti-wrinkle and anti-skin  
 actives, skin barrier repair actives, non-  
 steroidal cosmetic soothing actives, non-stearoidal anti-inflammatory  
 actives, topical anesthetics,  
 artificial tanning agents. . .

group  
 consisting of salicylic acid, benzoyl peroxide, 3-hydroxy benzoic acid,  
 glycolic acid, lactic acid, 4-  
 hydroxy benzoic acid, acetyl salicylic acid, niacinamide, cis-  
**retinoic acid**, trans-**retinoic acid**, **retinol**,  
 retinyl palmitate, 2-hydroxybutanoic acid, 2-hydroxypentanoic acid,  
 2-hydroxyhexanoic acid, cis-  
**retinoic acid**, trans-**retinoic acid**, **retinol**  
 , phytic acid, N-acetyl-L-cysteine, lipoic acid, azelaic acid,  
 arachidonic acid, benzoylperoxide, tetracycline, ibuprofen, naproxen,  
 hydrocortisone,  
 acetaminophen, resorcinol, phenoxyethanol, phenoxypropanol,  
 phenoxyisopropanol, 2,4,4'-tr ichloro-  
 2'-hydroxy diphenyl. . .

ACCESSION NUMBER: 1999013861 PCTFULL ED 20020515  
 TITLE (ENGLISH): CLEANSING AND CONDITIONING ARTICLE FOR SKIN OR HAIR  
 TITLE (FRENCH): ARTICLE NETTOYANT ET REVITALISANT POUR LA PEAU OU LES  
 CHEVEUX  
 INVENTOR(S): McATEE, David, Michael; NISSING, Nicholas, James;  
 HASENOEHRL, Erik, John; CABELL, David, William  
 PATENT ASSIGNEE(S): THE PROCTER & GAMBLE COMPANY  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9913861	A1	19990325
DESIGNATED STATES	AL AM AT AT AU AZ BA BB BG BR BY CA CH CN CU CZ CZ DE DE DK DK EE EE ES FI FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1998-IB1362	A	19980831
PRIORITY INFO.:	US 1997-60/058,608		19970912
	US 1998-60/072,440		19980126
	US 1998-60/085,495		19980514

DETD **Genistein** is a tyrosine kinase inhibitor and is under investigation for the I 0 treatment of diseases involving cellular proliferation. **Genistein** is practically insoluble in water.

Tretinoin is a **retinoic** acid that is being investigated as an anticancer agent. Tretinoin is practically insoluble in water.

As mentioned above, additional preferred drugs for inclusion in polymeric delivery systems include camptothecin, amphoterecin, nystatin, tretinoin,

**genistein**, and curcumin. Camptothecin is also an insoluble drug in aqueous solutions.

Tretinoin is a **retinoic** acid marketed as Retin-A (Registered in the name of McNeil Pharmaceutical Ltd.) for the treatment of **acne**. This agent increases membrane permeability in certain cell particles; the lysosomes, thereby releasing certain enzymes which may inhibit keratin formation and mucous metaplasia. **Retinoic** acid is also a cell-differentiating agent and is being explored as an anticancer agent.

**Genistein** is a tyrosine kinase inhibitor which leads to the inhibition of cell activation. Tyrosine kinases are signaling enzymes that promote cell surface receptors to transmit activation signals into the cell. Therefore, **genistein** may be used as an anti-inflammatory, anti-proliferative, anti-angiogenic or anticancer agent. Since this agent may detrimentally affect all cells systemically, localized application. . .

and Tretinoin were a kind gift from Dr. K. Wasan (University of B.C., Vancouver, B.C., Canada). All other hydrophobic drugs, including curcumin, **genistein**, tretinoin, nystatin, amphoterecin, and camptothecin were obtained from Sigma Chemicals (St. Louis, MO). Methotrexate and colchicine (Sigma Chemicals) were used as examples. . .

#### EXAMPLE 7

##### ASSESSMENT OF DRUG-DEPENDENT SOLIDIFICATION

Compositions containing 10% w/w drugs (methotrexate, colchicine, curcumin, **genistein**, tretinoin, nystatin, amphoterecin, camptothecin or paclitaxel) were manufactured using a 40:60 (TB:MEPEG'350) composition. Fifteen milligrams of each composition were placed in a 20. . .

therefore, failed to solidify in water at 37'C (Figure 6). However, paste compositions containing the highly hydrophobic and water insoluble drugs curcumin, **genistein**, tretinoin, nystatin, amphoterecin, camptothecin or

paclitaxel stayed intact for over 4 minutes under stirring, which indicated that these compositions had solidified. The . . .

Curcumin, **genistein**, tretinoin, nystatin, amphoterecin, camptothecin, and paclitaxel are described in The Merck Index as being insoluble in water. Studies by the present inventors. . .

100 0.038±0.01 8  
492nm Absorbance of controls = 0.47±0.05

#### EXAMPLE 9

##### DETERMINATION OF IN-VITRO DRUG RELEASE

Formulations containing 1 0% w/w drugs (methotrexate, colchicine, curcumin, **genistein**, tretinoin, nystatin, amphoterecin, camptothecin or paclitaxel) were manufactured using a 40:60 (TB:MePEG-'')50)1 composition. Formulations containing 2.5%, 5%, 10%, and 15% paclitaxel were. . .

**Genistein**, which has a very low water solubility (approximately 1 µg/mL), was released the fastest of all the hydrophobic drugs. However, only. . .

CLMEN. . . system of claim I wherein said hydrophobic drug is selected from the group consisting of amphotericin, anthralin, beclornethasone, betamethasone, camptothecin, curcumin, dexamethasone, indomethacin, **genistein**, lidocaine, insulin, nystatin, paclitaxel, tetracycline, tretinoin, cromoglycate, levobunolol, and terbinafine.

drug delivery system of claim 20 wherein said hydrophobic drug is selected from the group consisting of paclitaxel, camptothecin, amphoterecin, nystatin, tretinoin, **genistein**, and curcurnin.

ACCESSION NUMBER: 1999021908 PCTFULL ED 20020515  
TITLE (ENGLISH): POLYMERIC SYSTEMS FOR DRUG DELIVERY AND USES THEREOF  
TITLE (FRENCH): SYSTEMES POLYMERES DE LIBERATION DE MEDICAMENTS ET UTILISATION DE CES SYSTEMES  
INVENTOR(S): JACKSON, John; ZHANG, Xichen; BURT, Helen, M.  
PATENT ASSIGNEE(S): ANGIOTECH PHARMACEUTICALS, INC.; UNIVERSITY OF BRITISH COLUMBIA; JACKSON, John; ZHANG, Xichen; BURT, Helen, M.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9921908	A1	19990506
DESIGNATED STATES	AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1998-CA994	A	19981029
PRIORITY INFO.:	US 1997-60/063,721		19971029
	US 1998-60/076,842		19980304
	US 1998-09/181,582		19981028

DETD . . . are not limited to, dry skin, ichthyosis, paimar and plantar hyperkeratoses, dandruff, lichen simplex chronicus, Dariers disease, keratoses, lentigines, age spots, melasmas, blemished skin, **acne**, psoriasis, eczema, pruritis, inflammatory dermatoses, striae distensae (i.e. stretch marks), warts and calluses.

. . . with other cosmetic and pharmaceutical actives and excipients. Suitable other cosmetic and pharmaceutical agents include, but are not limited to, antifungals, vitamins, sunscreens, **retinoids**, antiallergenic agents, depigmenting agents, anti-inflammatory agents, anesthetics, surfactants, moisturizers, exfolients, stabilizers, preservatives, antiseptics, thickeners lubricants, humectants, chelating agents and skin penetration enhancers, as well as. . .

. . . to about 50 wt.%, and most preferably about 5 wt.-0o to about 20 wt.% of the oxa acids co-formulated with (i) **retinoids** such as **retinol**, **retinoic**

acid, retinyl palmitate, retinyl propionate, retinyl acetate, isotretinoin as well as synthetic **retinoid** mimics; (ii) hormonal compounds such as estriol, estradiol, estrone or conjugated estrogens; (iii)

20 alpha-hydroxyacids or polyhydroxy alpha-hydroxy acid such as glycolic acid, lactic acid, . . .

. . . the oxa acids in combination with antioxidants with phenolic hydroxy functions such as gallic acid derivataives (e.g. propyl galiate), bio-flavonoids (e.g. quercetin, rutin,

25 daidzein, **genistein**), ferrulic acid derivatives (e.g.

#### EXAMPLE 5

Cream for **Acne**, Skin Blemishes and Age Spots

This example illustrates a face cream than can be used to treat **acne**, skin blemishes and age spots.

wt.%

Phase A

oleic acid 1.0

stearic acid 17.0

polyoxyethylene (20 propylene glycol monostrearate) 10.0

**retinol** 0.1

Phase B

glycerine 5.0

2-pyrrolidone carboxylic acid 5.0

3,6,9-trioxadecanoic acid 7.5

3,6-dioxaheptanoic acid amide 2.5

lactic acid 3.0

demineralized water to 100.0

ammonium hydroxide to pH 4.2

All. . .

CLMEN 15 The composition of claim 1, further comprising at least one active selected from the group



consisting of antifungals, vitamins, sunscreens,  
retinoids, antiallergenic agents, depigmenting agents,  
anti-inflammatory agents, anesthetics, surfactants,  
moisturizers, exfolients, emulsifiers, stabilizers,  
39  
preservatives, antiseptics, emollients, thickeners,  
lubricants, humectants, chelating agents, fragrances,  
colorants and skin penetration.

the group consisting of  
dry skin, ichthyosis, palmar and plantar

48  
hyperkeratoses, dandruff, lichen simplex chronicus,  
Darriers disease, keratoses, lentigines, age spots,  
melasmas, blemished skin, acne, psoriasis, eczema,  
pruritis, inflammatory dermatoses, striae distensae,  
warts, calluses, signs of dermatological aging, skin  
wrinkles, fine wrinkles around the mouth area,  
irregular pigmentation, sallowness.

The method of claim 35, wherein said  
composition further comprises at least one active  
selected from the group consisting of antifungals,  
vitamins, sunscreens, retinoids, antiallergenic agents,  
depigmenting agents, anti-inflammatory agents,  
anesthetics, surfactants, moisturizers, exfolients,  
emulsifiers, stabilizers, preservatives, antiseptics,  
emollients, thickeners, lubricants, humectants,  
chelating agents, fragrances, colorants and skin  
penetration enhancers.

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ACCESSION NUMBER: 1997046231 PCTFULL ED 20020514  
TITLE (ENGLISH): OXA ACIDS AND RELATED COMPOUNDS FOR TREATING SKIN  
CONDITIONS  
TITLE (FRENCH): ACIDES OXA ET COMPOSES APPARENTES UTILISES DANS LE  
TRAITEMENT D'ETATS DERMATOLOGIQUES  
INVENTOR(S): PTCHHELINTSEV, Dmitri; SCANCARELLA, Neil; KALAFSKY,  
Robert  
PATENT ASSIGNEE(S): AVON PRODUCTS, INC.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:  
NUMBER KIND DATE  
-----  
WO 9746231 A1 19971211  
DESIGNATED STATES BR CA CN JP MX AT BE CH DE DK ES FI FR GB GR IE IT LU  
MC NL PT SE  
APPLICATION INFO.: WO 1997-US9281 A 19970602  
PRIORITY INFO.: US 1996-8/658,089 19960604

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DETD . . . are not limited to, dry  
skin, ichthyosis, palmar and plantar hyperkeratoses,  
8  
dandruff, lichen simplex chronicus, Darriers disease,  
keratoses, lentigines, age spots, melasmas, blemished  
skin, acne, psoriasis, eczema, pruritis, inflammatory  
dermatoses, striae distensae (i.e. stretch marks),  
warts and calluses.

combinations with other cosmetic and  
pharmaceutical actives and excipients. Suitable other

cosmetic and pharmaceutical agents include, but are not limited to antifungals, vitamins, sunscreens,

**retinoids**, anti-allergenic agents, depigmenting agents, 18

anti-inflammatory agents, anesthetics, surfactants, moisturizers, exfoliants, stabilizers, preservatives, antiseptics, thickeners, lubricants, humectants, chelating agents and skin penetration enhancers, as well as. . .

preferably from about

1 to about 50%, and most preferably about 5 to about 20% of the oxa diacids co-formulated with (i) **retinoids** such as **retinol**, **retinoic acid**, retinyl palmitate, retinyl propionate, retinyl acetate, isotretinoin as well as synthetic **retinoid** mimics; (ii) hormonal compounds such as estriol, estradiol, estrone or conjugated estrogens; (iii) alpha-hydroxyacids or polyhydroxy alpha-hydroxy acid such as glycolic acid, lactic acid, . . .

oxa diacids in combination with antioxidants with phenolic hydroxy functions such as gallic acid derivatives (e.g. propyl gallate), bio-flavonoids (e.g. quercetin, rutin, daidzein, **genistein**), ferrulic acid derivatives (e.g. ethyl ferrulate, sodium ferrulate), 6-hydroxy-2,5,7, tetra-, methylchroman carboxylic acid. The compositions may also contain effective concentrations of water soluble antioxidants such. . .

#### EXAMPLE 6

Cream for **Acne**, Skin Blemishes and Age Spots

This example illustrates a face cream that can be used to treat **acne**, skin blemishes and age spots.

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W/W%

Phase A

oleic acid 110

stearic acid 1740

polyoxyethylene (20 propylene glycol monostearate) 10\*0

**retinol** 0.1

Phase B

glycerine 5,0

2-pyrrolidone carboxylic acid 5,0

3,6,9-trioxaundecanedioic acid 7,5

3,6,9,12-tetraoxatetradecanedioic acid 2,5

lactic acid 3,0

demineralized water to 100,0

ammonium hydroxide to pH 4.2

All numbers. . .

CLMEN

15 The composition of claim 1, further

comprising at least one active selected from the group consisting of antifungals, vitamins, sunscreens,

**retinoids**, anti-allergenic agents, depigmenting agents, anti-inflammatory agents, anesthetics, surfactants, moisturizers, exfoliants, emulsifiers, stabilizers, preservatives, antiseptics, emollients, thickeners, lubricants, humectants, chelating agents, fragrances, colorants and skin penetration. . .

The method of claim 29, wherein said composition further comprises at least one active selected from the group consisting of antifungals, vitamins, sunscreens, **retinoids**, antiallergenic agents, depigmenting agents, anti-inflammatory agents, anesthetics, surfactants, moisturizers, exfolients, emulsifiers, stabilizers, preservatives, antiseptics, emollients, thickeners, lubricants, humectants, chelating agents, fragrances, colorants and skin penetration enhancers.

ACCESSION NUMBER: 1997039726 PCTFULL ED 20020514  
 TITLE (ENGLISH): OXA DIACIDS AND RELATED COMPOUNDS FOR TREATING SKIN CONDITIONS  
 TITLE (FRENCH): DIACIDE OXA ET COMPOSES VOISINS POUR TRAITER LES PROBLEMES DE PEAU  
 INVENTOR(S): PTCHELINTSEV, Dmitri; SCANCARELLA, Neil; KALAFSKY, Robert  
 PATENT ASSIGNEE(S): AVON PRODUCTS, INC.  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9739726	A1	19971030
DESIGNATED STATES	BR CA CN JP MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1997-US6973	A	19970425
PRIORITY INFO.:	US 1996-8/636,540		19960425

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DETD TABLE -1  
 FIRST COMPOSITION SECOND COMPOSITION  
 Cleanser Moisturizer  
 Cleanser Anti-acne preparation  
 Cleanser Moisturizer  
 Cleanser Facial Foundation  
 Moisturizer Toner  
 Cleanser Skin Lightener  
 Self-Tanner Cleanser  
 Cleanser Sunscreen  
 Skin Lightener Sunscreen  
 Sunscreen Anti-wrinkle Cream  
 Moisturizer Sunscreen  
 It is to be understood that this. . .

Suitable **retinoids** are **retinol**, **retinoic** acid or the CI@C20 esters of **retinol** and **retinoic** acid. Illustrative ceramides are Ceramide 1, Ceramide 2, Ceramide 3 and Ceramide 6.

Pseudoceramides may also be useful. Levels of **retinoids** and ceramides may suitably range from 0..00001 to 2%. preferably from 0.0001 to 0.1% by weight.

Anti-acne preparations will usually include an active selected from the group consisting of benzoyl peroxide, an alpha-hydroxycarboxylic acid, salicylic acid, **retinoids** and their derivatives. Amounts of these materials may suitably range from 0.1 to 30% by weight of the composition.

TABLE IV

CLEANSER  
 COMPONENT WEIGHT %  
 Glycerin 1.50  
 Polyoxyethylene 1.50  
 hydrogenated castor oil  
 Sorbitan stearate 1.00  
 Squalane 10.00  
 Dipropylene glycol 5.00

Genistein 0.10  
 water qs 10 0.00

TABLE V

SKIN-LIGHTENER  
 COMPONENT WEIGHT  
 Polysorbate 80 1.00  
 Ethyl alcohol 3.00  
 Polyethylene glycol-600 5.00  
 Citric acid 0.03  
 Sodium citrate 0.20  
 0-Ethyltetraacet@71glucosaniine. 0.10  
 Methylparaben 0.10  
 .Fragrance qs  
 Water qs. . .

CLMEN. . . independently include an active  
 material selected from the group consisting of alpha-  
 hydroxycarboxylic acid or salts thereof, beta-  
 hydroxycarboxylic acids or salts thereof, sunscreens,  
**retinoids**, ceramides, surfactants, self-tanners and  
 mixtures thereof.

ACCESSION NUMBER: 1996037420 PCTFULL ED 20020514  
 TITLE (ENGLISH): TREATMENT REGIME FOR SKIN  
 TITLE (FRENCH): CURE DE SOINS CUTANES  
 INVENTOR(S): SUARES, Alan, Joseph; NETTESHEIM, Susan; INDURSKY,  
 Michael; BERTOLINI, Peter  
 PATENT ASSIGNEE(S): UNILEVER PLC; UNILEVER N.V.  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9637420	A1	19961128
DESIGNATED STATES	AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1996-EP2274	A	19960524
PRIORITY INFO.:	US 1995-8/451,940		19950526
	US 1996-60/005,188		19960513

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 446-72-0 REGISTRY  
CN 4H-1-Benzopyran-4-one, 5,7-dihydroxy-3-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN **Genistein (6CI)**  
CN Isoflavone, 4',5,7-trihydroxy- (8CI)

OTHER NAMES:

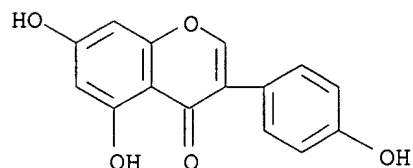
CN 4',5,7-Trihydroxyisoflavone  
CN 5,7,4'-Trihydroxyisoflavone  
CN Baichanin A  
CN C.I. 75610  
CN Genisteol  
CN Genisterin  
CN NPI 031L  
CN Prunetol  
CN SIPI 807-1  
CN Sophoricol  
FS 3D CONCORD  
MF C15 H10 O5  
CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*,  
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS,  
CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU,  
EMBASE, HODOC\*, IPA, MEDLINE, MRCK\*, NAPRALERT, NIOSHTIC, PIRA, PROMT,  
RTECS\*, SPECINFO, TOXCENTER, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*, NDSL\*\*, TSCA\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2814 REFERENCES IN FILE CA (1962 TO DATE)  
53 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
2836 REFERENCES IN FILE CAPLUS (1962 TO DATE)  
34 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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